Chapter 5. Integrated Health Effects

5.1. Mode of Action of CO Toxicity

5.1.1. Introduction

The diverse effects of CO are dependent upon concentration and duration of exposure as well as on the cell types and tissues involved. Responses to CO are not necessarily due to a single process and may instead be mediated by a combination of effects including COHb-mediated hypoxic stress and other mechanisms such as free radical production and the initiation of cell signaling. However, binding of CO to reduced iron in heme proteins with subsequent alteration of heme protein function is the common mechanism underlying the biological responses to CO.

5.1.2. Hypoxic Mechanisms

As discussed in the 2000 CO AQCD (U.S. EPA, 2000, 000907), the most well-known pathophysiologic effect of CO is tissue hypoxia caused by binding of CO to Hb. Not only does the formation of COHb reduce the O_2-carrying capacity of blood, but it also impairs the release of O_2 from O_2Hb. Compensatory alterations in hemodynamics, such as vasodilation and increased cardiac output, protect against tissue hypoxia. Depending on the extent of CO exposure, these compensatory changes may be effective in people with a healthy cardiovascular system. However, hemodynamic responses following CO exposure may be insufficient in people with decrements in cardiovascular function, resulting in health effects as described in Section 5.2.

The 2000 CO AQCD (U.S. EPA, 2000, 000907) reported changes in vasodilation due to CO levels between 500-2,000 ppm (Kanten et al., 1983, 011333; MacMillan, 1975, 012909). In one study, the vasodilatory response to CO in cerebral blood vessels was attributed to decreased O_2 availability (Koehler et al., 1982, 011341). In another study, exposure of rats to 1,000 ppm CO resulted in increased cerebral blood flow which was not triggered by tissue hypoxia since no changes in intramitochondrial NADH levels preceded vasodilation (Meilin et al., 1996, 079919). However, the response was blocked by the inhibition of NOS indicating a role for the free radical species NO in CO-mediated vasodilation (Meilin et al., 1996, 079919).

Increased cardiac output was also discussed in the 2000 CO AQCD (U.S. EPA, 2000, 000907) as a compensatory response to CO-mediated tissue hypoxia. Findings of studies which measured hemodynamic alterations following CO exposure were equivocal and sometimes contradictory (Penney, 1988, 012519). While most studies reported a positive correlation between COHb and cardiac output at COHb levels above 20%, one study demonstrated increased cardiac output in humans following acute exposure to 5% CO which resulted in the rapid rise in COHb levels to ~9% (Ayres et al., 1973, 193943). However, there was no increase in cardiac output following a more gradual increase in COHb levels to ~9% achieved by exposure to 0.1% CO over a longer period of time (Ayres et al., 1973, 193943). Increased heart rate and stroke volume (SV) were observed in response to CO exposure in one study (Stewart et al., 1973, 012428); however, some experiments found no change in SV in humans with 18-20% COHb (Vogel and Gleser, 1972, 010898) or 12.5% COHb (Klausen et al., 1968, 193936). The 2000 CO AQCD (U.S. EPA, 2000, 000907) reported that blood pressure was generally unchanged in human CO exposure studies, while a number of animal studies demonstrated CO-induced hypotension (Penney, 1988, 012519). No changes in forearm blood flow, blood pressure, or heart rate were reported in humans with approximately 8% COHb

Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at http://epa.gov/hero. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

(Hausberg and Somers, 1997, 083450). However, high-concentration exposures (3,000-10,000 ppm) in animals resulted in diminished organ blood flow (Brown and Piantadosi, 1992, 013441). In-depth discussion of hemodynamic changes resulting from CO exposure in recent human clinical studies can be found in Section 5.2.4.

Binding of CO to Mb, as discussed in the 2000 CO AQCD (U.S. EPA, 2000, 000907) and in Section 4.3.2.3, can also impair the delivery of O_2 to tissues. Mb has a high affinity for CO, about 25 times that of O_2; however, pathophysiologic effects are seen only after high-dose exposures to CO, resulting in COMb concentrations far above baseline levels. High-energy phosphate production in cardiac myocytes was inhibited when COMb concentrations exceeded 40%, corresponding to an estimated COHb level between 20-40% (Wittenberg and Wittenberg, 1993, 013909). Conversely, rat hearts perfused with solutions containing 6% CO (60,000 ppm) exhibited no change in high-energy phosphate production, respiration rate, or contractile function (Chung et al., 2006, 193987; Glabe et al., 1998, 086704).

5.1.3. Nonhypoxic Mechanisms

Nonhypoxic mechanisms underlying the biological effects of CO were discussed in the 2000 CO AQCD (U.S. EPA, 2000, 000907) and are summarized below. Most of these mechanisms are related to CO's ability to bind heme-containing proteins other than Hb and Mb (Raub and Benignus, 2002, 041616). Since then, additional experiments have confirmed and extended these findings. While the majority of the older studies utilized concentrations of CO far higher than ambient levels, many of the newer studies have employed more environmentally-relevant concentrations of CO.

5.1.3.1. Nonhypoxic Mechanisms Reviewed in the 2000 CO AQCD

Inhibition of heme-containing proteins such as cytochrome *c* oxidase and cytochrome P450 reductases may alter cellular function. CO interacts with the ferrous heme *a*3 of the terminal enzyme of the electron transport chain, cytochrome *c* oxidase (Petersen, 1977, 193764). Cytochrome *c* oxidase inhibition not only interrupts cellular respiration and energy production but can also enhance reactive oxygen species (ROS) production. In vivo studies observed CO binding to cytochrome *c* oxidase under conditions where COHb concentrations were above 50% (Brown and Piantadosi, 1992, 013441). It is unlikely that this could arise under physiologic conditions or under conditions relevant to ambient exposures.

A series of studies from the laboratory of Thom, Ischiropoulos and colleagues indicated that CO exposure produced a pro-oxidant cellular environment by liberation of NO. Exposure to CO concentrations of 10-20 ppm and above caused isolated rat platelets, as well as cultured bovine pulmonary endothelial cells, to release NO (Thom and Ischiropoulos, 1997, 085644). This response was blocked by treatment with an NOS inhibitor, indicating that the NO released was dependent on NOS activity. An increase in available NO was also seen in the lung and brain of CO-exposed rats (Ischiropoulos et al., 1996, 079491; Thom et al., 1999, 016757). Reaction of NO with superoxide to form the highly active oxidant species, peroxynitrite (Thom et al., 1997, 084337), was thought to lead to the activation and sequestration of leukocytes in brain vessels (Thom et al., 2001, 193779) and aorta (Thom et al., 1999, 016753), oxidation of plasma lipoproteins (Thom et al., 1999, 016753), and the formation of protein nitrotyrosine (Ischiropoulos et al., 1996, 079491; Thom et al., 1999, 016757; Thom et al., 1999, 016753). NO release by CO was attributed to the displacement of NO from nitrosyl-bound heme proteins. The rate of this event was slow; however, it occurred at environmentally-relevant concentrations of CO (Thom et al., 1997, 084337).

CO exposure also increased the production of other pro-oxidant species, including hydrogen peroxide (H_2O_2) and hydroxyl radical (OH). High-level CO exposure (2,500 ppm) increased OH in rat brain, and this response was distinct from tissue hypoxia (Piantadosi et al., 1997, 081326). The mechanism for enhanced H_2O_2 production was unclear. The release of H_2O_2 in the lung of CO-exposed rats was dependent upon the production of NO, as it was inhibited by pretreatment with an NOS inhibitor (Thom et al., 1999, 016757). It is possible that peroxynitrite formed after CO exposure inhibited electron transport at complexes I through III, or that cytochrome *c* oxidase inhibition led to mitochondrial dysfunction and ROS production.

Evidence was presented for CO-mediated vasorelaxation by three different mechanisms. First, CO may inhibit the synthesis of vasoconstrictors by P450 heme proteins (Wang, 1998, 086074).

Vasodilation in isolated vessels was demonstrated via this P450-dependent mechanism using high concentrations of CO (approximately 90,000 ppm) (Coceani et al., 1988, 040493). In the case of cytochrome P450 enzymes, tissue CO levels may need to be abnormally high to elicit a response since the Warburg binding coefficients (the ratio of CO to O_2 at which half the reactive sites are occupied by CO) for cytochrome P450s range from 0.1-12 (Piantadosi, 2002, 037463). P450 inhibition may reduce the hypoxia-induced expression of mitogens such as erythropoietin (EPO), vascular endothelial growth factor (VEGF), endothelin-1 (ET-1), and platelet derived growth factor (PDGF), which may decrease smooth muscle proliferation in response to hypoxia (Wang, 1998, 086074). CO also interfered with the metabolism of barbiturates and other drugs; however, this was probably due to the hypoxic actions of CO rather than to P450 inhibition (Roth and Rubin, 1976, 012703; Roth and Rubin, 1976, 012420).

Secondly, CO has been shown to play a physiological role in vasomotor control and in signal transduction by activation of soluble guanylate cyclase (sGC), causing a conversion of GTP to cyclic GMP (cGMP). CO reversibly ligates the heme core of sGC, and the resulting protoporphyrin IX intermediate triggers cGMP production (Ndisang et al., 2004, 180425). CO caused vascular relaxation, independent of the endothelium, in human arterial rings (Achouh et al., 2008, 179918), rat tail artery (Wang et al., 1997, 084341), and rat thoracic aorta (Lin and McGrath, 1988, 012773), but not in cerebral vessels (Andresen et al., 2006, 180449; Brian et al., 1994, 076283). Activation of sGC by CO has been linked to neurotransmission, vasodilation, bronchodilation, inhibition of platelet aggregation, and inhibition of smooth muscle proliferation (Brüne and Ullrich, 1987, 016535; Cardell et al., 1998, 086700; Cardell et al., 1998, 011534; Morita et al., 1997, 085345; Verma et al., 1993, 193999).

CO-mediated vasorelaxation can also be caused by activation of voltage- or Ca^{2+}-activated potassium (K^+) channels in smooth muscle cells, which leads to membrane hyperpolarization, voltage-dependent Ca^{2+} channel closing, reduction of resting Ca^{2+} concentration and vascular tissue relaxation (Farrugia et al., 1993, 013826; Wang et al., 1997, 084341). This effect may be linked to sGC activity; however, it has also been reported to occur independently (Dubuis et al., 2003, 180439; Naik and Walker, 2003, 193852). Developmental stage and tissue type will determine whether K^+ channels or the sGC/cGMP pathway play more of a role in vasorelaxation (Ndisang et al., 2004, 180425).

Collectively, these older studies demonstrated that exposures to high concentrations of CO resulted in altered functions of heme proteins other than Hb and Mb. Decreased cellular respiration and energy production and increased ROS following cytochrome *c* oxidase inhibition would likely predispose towards cellular injury and death. The release of NO from sequestered stores could contribute to the pro-oxidant status if superoxide levels are simultaneously increased. Furthermore, increased ROS and reactive nitrogen species are known to promote cell signaling events leading to inflammation and endothelial dysfunction. An inappropriate increase in vasorelaxation due to inhibition of vasoconstrictor production or to activation of vasodilatory pathways (sGC and ion channels) could potentially limit compensatory alterations in hemodynamics. Alternatively, CO-binding to sGC could result in decreased vasorelaxation by interfering with the binding of NO to sGC. NO can also activate sGC, and with a 30-fold greater affinity than CO, is 1,000-fold more potent with respect to vasodilation and sGC activation (Stone and Marletta, 1994, 076455). CO could further contribute to endothelial dysfunction by this mechanism. Although the 2000 CO AQCD (U.S. EPA, 2000, 000907) made no definitive links between these nonhypoxic mechanisms of CO and CO-mediated health effects, it did document the potential for CO to interfere with basic cellular and molecular processes that could lead to dysfunction and/or disease.

5.1.3.2. Recent Studies of Nonhypoxic Mechanisms

Since the 2000 CO AQCD (U.S. EPA, 2000, 000907), new studies have provided additional evidence for nonhypoxic mechanisms of CO which involve the binding of CO to reduced iron in heme proteins. These mechanisms, which may be interrelated, are described below and include:

- Alteration in NO signaling
- Inhibition of cytochrome c oxidase
- Heme loss from protein

- Disruption of iron homeostasis
- Alteration in cellular redox status

Recent studies have also demonstrated nonhypoxic mechanisms of CO which are either indirectly linked to heme protein interactions or not yet understood. These mechanisms are described below and include:

- Alteration in ion channel activity
- Modulation of protein kinase pathways

This assessment evaluates these nonhypoxic mechanisms in terms of their potential to contribute to health effects associated with environmentally-relevant CO exposures. As discussed above, CO at high concentrations may promote oxidative stress, cell injury and death, inflammation and endothelial dysfunction. Whether lower CO concentrations trigger these same processes is of key interest since they may potentially contribute to adverse health effects following ambient exposures.

In addition, a large number of studies published since the 2000 CO AQCD (U.S. EPA, 2000, 000907) have focused on the role of CO derived from HO-catalyzed heme metabolism as an endogenous signaling molecule and on the potential therapeutic effects of exogenous CO administered at high concentrations. This assessment addresses aspects of these topics pertaining to the evaluation of health effects associated with environmentally-relevant CO exposures.

Alteration in NO Signaling

Work by Thorup et al. (1999, 193782) demonstrated altered NO signaling in isolated rat renal resistance arteries. In one set of experiments, rapid release of NO was observed in response to exogenous CO. This response was biphasic, peaking at 100 nM CO in the perfusate and declining at higher concentrations. It was also NOS-dependent as it required L-arginine and was blocked by a NOS inhibitor. The authors attributed the effects of CO on NO release to either stimulated eNOS or to displacement of preformed NO from intracellular binding sites. These findings are similar to those of Thom and colleagues (Ischiropoulos et al., 1996, 079491; Thom and Ischiropoulos, 1997, 085644; Thom et al., 1994, 076459; Thom et al., 1997, 084337; Thom et al., 1999, 016753; Thom et al., 1999, 016757; Thom et al., 2000, 011574; Thom et al., 2006, 098418) who demonstrated NO release, presumably from sequestered stores in platelets, endothelial cells, aorta and lung in response to CO (see above). Furthermore in a second set of experiments, Thorup et al. (1999, 193782) demonstrated inhibition of agonist-stimulated NOS activity in isolated rat renal resistance arteries. Here rapid NOS-dependent release of NO following carbachol stimulation was blocked by pretreatment with 100 nM CO or by upregulation of intracellular HO-1. Additional experiments using blood-perfused isolated juxtamedullary afferent arterioles demonstrated a biphasic response to CO with rapid vasodilation observed at lower, but not higher, concentrations of CO. These same higher concentrations of CO inhibited agonist-stimulated vasodilation in the arterioles. In order to determine whether CO had a direct effect on the activity of NOS, which is a heme protein, purified recombinant eNOS was exposed in vitro to CO in the presence of the necessary substrates and cofactors. A dose-dependent inhibition of NOS by CO was observed, suggesting that CO-mediated NO release in the isolated vessels was not due to stimulated NOS activity. The authors concluded that CO effects on vascular tone were due to the liberation of NO from intracellular binding sites at lower concentrations and to the inhibition of NOS at higher concentrations.

These findings illustrate the potential of CO to alter processes dependent on endogenous NO either by enhancing intracellular concentrations of free NO (increased vasodilatory influence) or by inhibiting agonist-induced NO production by NOS (decreased vasodilatory influence). In addition, CO may compete with NO for binding to sGC as discussed above. Since NO activates sGC to a greater extent than CO, NO-dependent vasodilation may be significantly impaired in the presence of CO. In fact, a recent study in transgenic mice demonstrated that chronic overexpression of HO-1 in vascular smooth muscle resulted in attenuated NO-mediated vasodilation and elevated blood pressure (Imai et al., 2001, 193864). Results of this study suggested that decreased sensitivity of sGC to NO contributed to the changes in vascular function. The considerations mentioned above, however, do not preclude an important role for CO in maintaining vasomotor tone in vessels where

CO and NO do not compete for available heme sites on sGC. This could occur when both mediators are present at low concentrations compared with sGC or in situations where NOS does not co-localize with sGC, as discussed by Thorup et al. (1999, 193782).

Inhibition of Cytochrome *c* Oxidase

High concentrations of CO are known to inhibit cytochrome c oxidase, the terminal enzyme in the mitochondrial electron transport chain, resulting in inhibition of mitochondrial respiration and the formation of superoxide from mitochondrial substrates. Several recent studies demonstrated CO-mediated decreases in cytochrome *c* oxidase activity in model systems ranging from isolated mitochondria to whole animals. In a study by Alonso et al. (2003, 193882), exposure of isolated mitochondria from human skeletal muscle to 50-500 ppm CO for 5 min decreased cytochrome *c* oxidase activity. Similarly, exposure of cultured macrophages to 250 ppm CO for 1 h inhibited cytochrome *c* oxidase (Zuckerbraun et al., 2007, 193884). In this latter study, increased ROS were observed following exposure to 250 ppm CO, as well as to CO concentrations as low as 50 ppm, for 1 h. Animal studies demonstrated that exposure of rats to 250 ppm CO for 90 min inhibited cytochrome *c* oxidase activity in myocardial fibers (Favory et al., 2006, 184462). Exposure of mice to 1,000 ppm CO for 3 h, resulting in COHb levels of 61%, decreased cytochrome *c* oxidase activity in heart mitochondria (Iheagwara et al., 2007, 193861).

Heme Content Loss from Proteins

In addition to decreasing the activity of cytochrome *c* oxidase, exposure of mice to 1,000 ppm CO for 3 h resulted in decreased protein levels and heme content of cytochrome *c* oxidase in heart mitochondria (Iheagwara et al., 2007, 193861). CO-mediated heme release was also seen in a study by Cronje et al. (2004, 180440) and was followed by increased endogenous CO production through the activation of HO-2 and the induction of HO-1. Loss of heme from proteins leads to loss of protein function and often to protein degradation.

Disruption of Iron Homeostasis

Exposure of rats to 50 ppm CO for 24 h increased levels of iron and ferritin in the bronchoalveolar lavage fluid (BALF), decreased lung non-heme iron and increased liver non-heme iron (Ghio et al., 2008, 096321). Furthermore in this same study, exposure of cultured human respiratory epithelial cells to 10-100 ppm CO for 24 h caused a dose-dependent decrease in cellular non-heme iron and ferritin. Heme loss, which was observed in other studies (Cronje et al., 2004, 180440; Iheagwara et al., 2007, 193861), may also contribute to disruption of iron homeostasis. Iron homeostasis is critical for the sequestration of free iron and the prevention of iron-mediated redox cycling which leads to ROS generation and lipid peroxidation.

Alteration in Cellular Redox Status

Recent studies demonstrated that exposure to low, moderate, and high levels of CO increased cellular oxidative stress in cultured cells (Kim et al., 2008, 193961; Zuckerbraun et al., 2007, 193884). A dose-dependent increase in dichlorofluorescein (DCF) fluorescence (an indicator of ROS) occurred following 1-h exposure to 50-500 ppm CO in macrophages and following 1-h exposure to 250 ppm CO in hepatocytes. NOS inhibition had no effect on the increase in DCF fluorescence in CO-treated macrophages, indicating that the effects were not due to an interaction of CO and NO (Zuckerbraun et al., 2007, 193884). Mitochondria were identified as the source of the increased ROS since mitochondria-impaired cells (rho zero cells and treatment with antimycin A) did not respond to CO with an increase in DCF fluorescence. Furthermore, 1-h exposure to 250 ppm CO inhibited mitochondrial cytochrome *c* oxidase enzymatic activity in macrophages (Zuckerbraun et al., 2007, 193884). Recently, inhibition of cytochrome *c* oxidase was demonstrated in HEK-293 cells transfected with HO-1 and in macrophages with induced HO-1; this effect was attributed to

endogenously produced CO (D'Amico et al., 2006, 193992). In hepatocytes, exposure to 250 ppm CO for 1 h resulted in Akt phosphorylation and nuclear translocation of nuclear factor kappa B (NF-κB), effects which were blocked by antioxidants (Kim et al., 2008, 193961). Significant increases in apoptosis were also observed in this model. Thus in this study, CO exposure led to uncoupled mitochondrial respiration and ROS-induced programmed cell death.

Further evidence for cellular redox stress is provided by studies in which glutathione stores were altered following CO exposure in vitro (Kim et al., 2008, 193961; Patel et al., 2003, 043155). In addition, mitochondrial redox stress was observed in livers of rats exposed to 50 ppm CO (Piantadosi et al., 2006, 180424). Furthermore, an adaptive increase in intracellular antioxidant defenses (i.e., superoxide dismutase) was observed in endothelial cells exposed to 10 ppm CO for 40 min (Thom et al., 2000, 011574), and mitochondrial biogenesis was observed in hearts of mice exposed to 250 ppm CO for 1 h (Suliman et al., 2007, 193768).

Several mechanisms could contribute to the cellular redox stress elicited by CO exposure. First, inhibition of cytochrome *c* oxidase could result in increased mitochondrial superoxide generation. Secondly, interactions of CO with heme proteins could lead to the release of heme and free iron and subsequently to the generation of ROS. As mentioned above, increased ROS generation has been linked to cellular injury and death, inflammation, and endothelial dysfunction.

Two of the above-mentioned studies demonstrated that CO-mediated mechanisms were unrelated to hypoxia by showing that hypoxic conditions failed to mimic the results obtained with CO. Hence, the mitochondrial redox stress and mitochondrial pore transition observed in livers from rats exposed to CO (Piantadosi et al., 2006, 180424) and the cardiac mitochondrial biogenesis observed in mice exposed to CO (Suliman et al., 2007, 193768) were attributed specifically to nonhypoxic mechanisms of CO.

Alteration in Ion Channel Activity

Work by Dubuis et al. (Dubuis et al., 2002, 193911) demonstrated increased current through Ca^{2+}-activated K^{+} channels in smooth muscle cells from pulmonary arteries of rats exposed to 530 ppm CO for 3 wk. These findings provide further evidence for non-cGMP-dependent vasodilatory actions of CO.

Modulation of Protein Kinase Pathways

Endogenously produced CO is a gaseous second messenger molecule in the cell. Work from numerous laboratories has demonstrated the potential for CO to be used as a therapeutic gas with numerous possible clinical applications since it can produce anti-inflammatory, anti-apoptotic, and anti-proliferative effects (Durante et al., 2006, 193778; Ryter et al., 2006, 193765). These studies generally involved pretreatment with CO followed by exposure to another agent 12-24 h later. There is extensive literature on this topic as reviewed by Ryter et al. (2006, 193765), Durante et al. (2006, 193778) and others. A number of these processes are mediated through cGMP while others involve redox-sensitive kinase pathways, possibly secondary to CO-dependent generation of ROS. For example, 250 ppm CO inhibited growth of airway smooth muscle cells by attenuating the activation of the extracellular signal-regulated kinase 1/2 (ERK 1/2) pathway, independent of sGC and other MAP kinases (Song et al., 2002, 037531). A second example is provided by the study of Kim et al. (2005, 193959) where 250 ppm CO inhibited PDGF- induced smooth muscle cell proliferation by upregulating $p21^{Waf1/Cip1}$ and caveolin-1, and down-regulating cyclin A expression. In this case, effects were dependent upon cGMP and the p38 MAPK pathway (Kim et al., 2005, 193959). Thirdly, rat endothelial cells exposed to 15 ppm CO escaped anoxia/reoxygenation-induced apoptosis via modulation of the signaling pathways involving phosphoinositide 3-kinase (PI3K), Akt, p38 MAP kinase, Signal Transducers and Activators of Transcription (STAT-1) and STAT-3 (Zhang et al., 2005, 184460). In a fourth study, Akt was found to be responsible for the CO-induced activation of NF-κB, protecting against hepatocyte cell death (Kim et al., 2008, 193961). While research focusing on therapeutic applications of CO generally involves high-level short-term exposure to CO (i.e., 250-1,000 ppm for up to 24 h), some studies found effects below 20 ppm (Zhang et al., 2005, 184460). Few if any studies on the therapeutic effects of CO have explored the dose-response relationship

between CO and pathway activation/deactivation, so it remains unclear how these effects may be related to environmentally-relevant exposures.

Concentration-Response Relationships

In many cases, the concentrations of exogenous CO required for these nonhypoxic effects were much higher (Alonso et al., 2003, 193882; Favory et al., 2006, 184462; Iheagwara et al., 2007, 193861; Thorup et al., 1999, 193782) than concentrations of CO in ambient air. However, in some studies the effects were mimicked by upregulation of HO-1 which would result in increased local production of CO as well as of iron and biliverdin (D'Amico et al., 2006, 193992; Imai et al., 2001, 193864; Thorup et al., 1999, 193782). For example, HO-1 upregulation or overexpression attenuated carbachol-mediated NO release and NO-mediated vasodilation, similar to the effects of exogenous CO in these same models (Imai et al., 2001, 193864; Thorup et al., 1999, 193782). In the study by D'Amico et al. (2006, 193992), overexpression of HO-1 in cells inhibited cellular respiration by 12% and decreased cytochrome c oxidase activity by 23%. It is not clear how comparable these conditions involving increased intracellular concentrations of endogenous CO are to increased intracellular concentrations of CO resulting from exogenous CO exposures. Neither is it clear what concentrations of intracellular CO are generated locally within cells as a result of HO-catalyzed heme metabolism. However, a small amount of a relatively high local concentration of endogenous CO produced in a regulated manner by HO-1 and HO-2 may be sufficient to react with local targets (e.g., heme proteins), while a larger amount of exogenous CO may be required to reach the same targets. This may be due to indiscriminate reactions of exogenous CO with other target proteins or to other issues related to compartmentalization. It is conceivable that acute or chronic exposures to ambient CO could "sensitize" (or "desensitize") targets of endogenous cellular CO production, but there is no experimental evidence to support this mechanism.

There is a growing appreciation that nonhypoxic mechanisms may contribute to the effects associated with CO toxicity and poisoning (Ischiropoulos et al., 1996, 079491; Thom et al., 1994, 076459; Weaver et al., 2007, 193939). On the other hand, recent studies suggest that exogenous CO at lower concentrations may have beneficial anti-inflammatory, anti-proliferative and cytoprotective effects under certain circumstances (Durante et al., 2006, 193778; Ryter et al., 2006, 193765). Since the focus of this assessment is on mechanisms which are relevant to ambient exposures, it is important to understand which mechanisms may occur at "low" (50 ppm and less) and "moderate" (50-250 ppm CO) concentrations of CO. Hence, both recent animal studies and relevant older ones which add to the understanding of mechanisms in this range of CO concentrations are briefly summarized in Table 5-1. It should be noted that most of the above-mentioned nonhypoxic mechanisms were demonstrated at CO concentrations of 50 ppm and less.

Table 5-1. Responses to CO exposures at low and moderate concentrations.

Study	Model System	CO Exposure	Response	Notes
IN VITRO				
Alonso et al. (2003, 193882)	Human muscle mitochondria	50, 100, 500 ppm 5 min	Decreased cytochrome c oxidase activity	
Thom and Ischiropoulos (1997, 085644)	Rat platelets	10 ppm	Increased free NO	
Thom et al. (1997, 084337)	Bovine pulmonary artery endothelial cells	20 ppm 30-60 min	Increased free NO and peroxynitrite	Reported to correspond to 7% COHb
Thom et al. (2000, 011574)	Bovine pulmonary artery endothelial cells	10 ppm 40 min	Increased MnSOD and protection against toxic effects of 100 ppm CO	Adaptive responses
Song et al. (2002, 037531)	Human aortic smooth muscle cells	50-500 ppm 24 h	Inhibition of cellular proliferation	Blocked activation of ERK1/2 pathway, independent of sGC and other MAP kinases
Kim et al. (2005, 193959)	Rat pulmonary artery smooth muscle cells	250 ppm 1 h	Inhibited PDGF- induced smooth muscle cell proliferation	Upregulated $p21^{Waf1/Cip1}$ and caveolin-1, and down-regulated cyclin A expression.
Kim et al. (2008, 193961)	Rat hepatocytes	250 ppm 1 h 2x per day 250 ppm 1 h	Blocked spontaneous apoptosis Increased mitochondrial ROS generation, increased mitochondrial glutathione oxidation, and decreased cellular ascorbic acid	CO induced Akt phosphorylation via ROS production CO activated NFκB
Zhang et al. (2005, 184460)	Rat pulmonary artery endothelial cells	15 ppm 0.5-24 h	Blocked anoxia-reoxygenation mediated apoptosis	Modulation of PI3K/Akt/p38 MAP kinase and STAT-1 and STAT-3
Zuckerbraun et al. (2007, 193884)	Mouse macrophages	50 and 250 ppm 1 h	Increased ROS generation (dose dependent response for 50-500 ppm CO)	Mitochondrial derived ROS and cytochrome c oxidase inhibition demonstrated for 250 ppm
Ghio et al. (2008, 096321)	Human bronchial epithelial cells	10-100 ppm 24 h	Dose-dependent decrease in cellular non-heme iron (effect at 10 ppm was significant, effect at 50 ppm maximal) Dose-dependent decrease in cellular ferritin at 50-100 ppm 50 ppm blocked iron uptake by cells 50 ppm increased iron release from cells	Compare with in vivo experiments in same paper
IN VIVO				
Ghio et al. (2008, 096321)	Rats	50 ppm 24 h	Mild neutrophil accumulation in BALF Increased lavage MIP-2, protein, LDH Lavage iron and ferritin were increased by CO Lung non-heme iron was decreased by CO Liver non-heme iron was increased by CO	Compare with in vitro experiments in same paper
Thom et al. (1999, 016753)	Rats	50 ppm 1 h 100 ppm 1 h	Increased nitrotyrosine in aorta Leukocyte sequestration in aorta after 18 h Albumin efflux from skeletal muscle microvasculature 3 h after CO LDL oxidation	Effects blocked by NOS inhibitor
Thom et al. (1999, 016757)	Rats	100 ppm 1 h 50 ppm 1 h	Elevated free NO during CO exposure (EPR) Elevated nitrotyrosine in lung homogenates Lung capillary leakage 18 h after exposure	Inhibition of NOS abrogated CO effects
Sorhaug et al. (2006, 180414)	Rats	200 ppm 72 wk	No changes in lung morphology No pulmonary hypertension No atherosclerotic lesions in systemic vessels Ventricular hypertrophy	
Loennechen et al. (1999, 011549)	Rats	100 and 200 ppm 1-2 wk	Increased ET-1 mRNA in the heart ventricles, increased right and left ventricular weight	12 and 23% COHb
Favory et al. (2006, 184462)	Rats	250 ppm 90 min	Complex IV inhibition in myocardial fibers Inhibition of vasodilatory response to acetylcholine and SNP, Increased coronary perfusion pressure and contractility	11% COHb
Piantadosi et al. (2006, 180424)	Rats	50 ppm CO or hypobaric hypoxia for 1, 3, or 7 days	Liver mitochondrial oxidative and nitrosative stress, altered mitochondrial permeability pore transition sensitivity	CO effects not mimicked by hypobaric hypoxia
Suliman et al. (2007, 193768)	Mice	250 ppm 1 h	Cardiac mitochondrial biogenesis	Activation of GC involved. No role for NOS. Increased mitochondrial H_2O_2 and activation of Akt proposed
Wellenius et al. (2004, 087874)	Rats Model of MI	35 ppm 1 h	Decreased delayed ventricular beat frequency	Altered arrhythmogenesis
Wellenius et al. (2006, 156152)	Rats Model of MI	35 ppm 1 h	Decreased supraventricular ectopic beats	Altered arrhythmogenesis

Study	Model System	CO Exposure	Response	Notes
Carraway et al. (2002, 026018)	Rats Model of hypoxic pulmonary vascular remodeling	Hypobaric hypoxia ± 50 ppm CO 3 wk	CO promoted remodeling and increased pulmonary vascular resistance	
Gautier et al. (2007, 096471)	Rats Model of right ventricle hypertrophy secondary to chronic hypoxia	3 wk of hypobaric hypoxia with 50 ppm CO during last week	Rats with pulmonary hypertension were more sensitive to CO which altered the right ventricular adaptive response to pulmonary hypertension leading to ischemic lesions	
Melin et al. (2005, 193833)	Rats Model of right ventricle hypertrophy secondary to chronic hypoxia	50 ppm 10 wk	CO increased cardiac dilation and decreased left ventricular function	
Melin et al. (2002, 037502)	Rats Model of right ventricle hypertrophy secondary to chronic hypoxia	50 ppm 10 wk	CO increased right ventricular hypertrophy, decreased right ventricular diastolic function and increased left ventricular weights	

5.1.3.3. Implications of Nonhypoxic Mechanisms

A key issue in understanding the biological effects of environmentally-relevant exposures to CO is whether the resulting partial pressures of CO (pCO) in cells and tissues can initiate cell signaling which is normally mediated by endogenously generated CO or perturb signaling which is normally mediated by other signaling molecules such as NO.

Several aspects need to be considered. First of all, during a period of exogenous CO uptake, Hb acts as a buffer for most cells and tissues by limiting the availability of free CO. Nevertheless, COHb delivers CO to cells and tissues. This delivery involves CO's dissociation from Hb followed by its diffusion down a pCO gradient. Hence, greater release of CO from COHb will occur under conditions of low cell/tissue pCO. Conversely, higher cell/tissue pCO in cells/tissues than in the blood will lead to the egress of CO from cells/tissues.

A second consideration is the role played by O_2 in competing with CO for binding to intracellular heme protein targets. In general, heme proteins (e.g., cytochrome *c* oxidase) are more sensitive to CO when O_2 is limited. Hence, hypoxic conditions would be expected to enhance the effects of CO. This concept is demonstrated in the study by D'Amico et al. (2006, 193992). NO, which also competes with O_2 and CO for binding to heme proteins, may have a similar impact.

A third consideration is whether certain cell types serve as primary targets for the effects of CO. Besides the blood cells (including leukocytes and platelets), the first cells encountering CO following its dissociation from Hb are the endothelial cells which line blood vessels. An exception to this situation is in the lungs where epithelial and inflammatory cells found in airways and alveoli are exposed to free CO prior to CO binding to Hb. These lung cells may also serve as unique targets for CO. Processes such as pulmonary microvascular endothelial dysfunction, inflammatory cell activation, and respiratory epithelial injury may ensue as a result of preferential targeting of these cell types.

Since there is potential for exogenous CO to affect endogenous pools of CO, the concentrations of CO in cells and tissues before and after exogenous exposures are of great interest. Table 5-2 summarizes findings from four recent studies relevant to this issue. It should be noted that exposure to 50 ppm CO resulted in a three- to fivefold increase in tissue CO concentration.

Table 5-2. Tissue concentration of CO following inhalation exposure.

Study	CO Exposure	Tissue CO Concentrations	COHb	Notes
Cronje et al. (2004, 180440)	Rat 2,500 ppm 45 min	Blood: 27,500 (800) pmol/mg Heart: 800 (300) pmol/mg Muscle: 90 (80) pmol/mg Brain: 60 (40) pmol/mg Control levels in parentheses	66-72%	CO concentration increased in the heart but not in brain or skeletal muscle after CO exposure A later report stated that these tissue CO values were too high due to a computational error (Piantadosi et al., 2006, 180424)
Vreman et al. (2005, 193786)	Mice 500 ppm 30 min	Blood: 2648 ± 400 (45) pmol/mg Heart: 100 ± 18 (6) pmol/mg Muscle: 14 ± 1 (10) pmol/mg Brain: 18 ± 4 (2) pmol/mg Kidney: 120 ± 12 (7) pmol/mg Spleen: 229 ± 55 (6) pmol/mg Liver: 115 ± 31 (5) pmol/mg Lung: 250 ± 2 (3) pmol/mg Intestine: 9 ± (4) pmol/mg Testes: 6 ± 3 (2) pmol/mg Control levels in parentheses	28%	CO concentration relative to 100% blood: Lung: 9.4% Spleen: 8.6% Kidney: 4.5% Liver: 4.3% Heart: 3.8% Brain: 0.7% Muscle: 0.5% Intestine: 0.3%, Testes: 0.2%
Piantadosi et al. (2006, 180424)	Rats 50 ppm 1-7 days	Liver: 30-40 pmol/mg Control liver 10 pmol/mg	4-5% Control 1%	CO concentration reached a plateau after 1 day
Vreman et al. (2005, 193786)	Mice 50, 250 and 1,250 ppm 1 h	Heart (left ventricle) 50 ppm: 50 pmol/mg 250 ppm: 95 pmol/mg 1250 ppm: 160 pmol/mg Control heart: 9 pmol/mg		No mention of COHb% but exposures were similar to those in Cronje et al. (2004, 180440)

Data is expressed as pmol CO/mg tissue wet weight

Furthermore, endogenous CO production is known to be increased during inflammation, hypoxia, increased heme availability and other conditions of cellular stress where HO-1 or HO-2 activity is increased. A few studies reported cell and tissue concentrations of CO along with accompanying COHb levels resulting from enhanced endogenous CO production; Table 5-3 summarizes these findings. Additional measurements of CO levels in cells and tissues following increased endogenous production and following inhalation of exogenous CO may provide further insight into the relationship between the CO tissue concentration and biological responses.

Table 5-3. Tissue concentration of CO following increased endogenous production.

Study	Exposure	Tissue CO	COHb	Notes
Carraway et al. (2000, 021096)	Rats Hypobaric hypoxia for 21 days		1.5-2.8% Control 0.5%	COHb highest after days 1 and 21 at three- to fourfold higher than controls
Piantadosi et al. (2006, 180424)	Rats Hypobaric hypoxia 1-7 days	Liver: 5-12 pmol/mg Control liver 10 pmol/mg	1-1.25% Control 1%	CO concentration reached a plateau after 1 day
Vreman et al. (2005, 193786)	Mice 30 μM heme	Blood: 88 ± 10 (45) pmol/mg Heart: 14 ± 3 (6) pmol/mg Muscle: 7 ± 1 (10) pmol/mg Brain: 2 ± 0 (2) pmol/mg Kidney: 7 ± 2 (7) pmol/mg Spleen: 11 ± 1 (6) pmol/mg Liver: 8 ± 3 (5) pmol/mg Lung: 8 ± 3 (3) pmol/mg Intestine: 3 ± 1 (4) pmol/mg Testes: 2 ± 0 (2) pmol/mg Control levels in parentheses	0.9%	CO concentration relative to 100% blood: Heart: 16% Spleen: 13% Lung: 9% Liver: 9% Kidney: 8% Muscle: 8% Intestine: 3% Brain: 2% Testes: 2%

Data is expressed as pmol CO/mg tissue wet weight

It should be noted that increased cellular and tissue concentrations of biliverdin and iron accompany the increased endogenous production of CO by HO-1 and HO-2. Biliverdin and iron have known biological effects, with biliverdin exhibiting antioxidant properties and iron exhibiting pro-oxidant properties (Piantadosi et al., 2006, 180424), which could complicate interpretation of results from studies in which HO-1 and HO-2 activities are increased. In addition, indiscriminate reactions occurring in the case of exogenous CO would likely lead to less specific responses than those mediated by reactions of endogenously-produced CO with local targets. Hence, the situations of increased endogenous CO production and of exogenous CO exposure are not equivalent.

A further consideration is that in the numerous conditions and disease states where HO-1 is induced, increased levels of endogenously produced CO may represent an adaptive response to stress (Durante et al., 2006, 193778; Piantadosi, 2008, 180423). These increases and the accompanying increases in COHb generally fall in the range of 1.5- to 4-fold, with the exception of some situations of hemolytic anemia and hemoglobin disorders (see Figure 4-11 for results in humans). The resulting excess endogenous CO may react intracellularly with heme proteins or diffuse into the blood according to the gradient of pCO in the cell/tissue and blood compartments. In many cases, beneficial effects or compensatory mechanisms may result as a result of short-term induction of HO-1, as reviewed by Ryter et al. (2006, 193765) and Durante et al. (2006, 193778). Longer term increases in HO-1 are sometimes associated with protective responses, as in the case of atherosclerosis (Cheng et al., 2009, 193775; Durante et al., 2006, 193778), and sometimes with pathophysiologic responses as demonstrated in hypoxic pulmonary vascular remodeling (Carraway et al., 2002, 026018) and models of salt-sensitive hypertension (Johnson et al., 2003, 193868; Johnson et al., 2004, 193870) and metabolic syndrome (Johnson et al., 2006, 193874). Increased endogenous CO in hearts of individuals with ischemic heart disease and in lungs of individuals with various forms of inflammatory lung disease might also be expected (Scharte et al., 2006, 194115; Yamaya et al., 1998, 047525; Yasuda et al., 2005, 191953) (Figure 4-12). It is conceivable that prolonged increases in endogenous CO production in chronic disease states may result in less of a reserve capacity to handle additional intracellular CO resulting from exogenous exposures, but there is no experimental evidence to support this mechanism. Perhaps these circumstances lead to dysregulated functions or toxicity. Thus, CO may be responsible for a continuum of effects from cell signaling to adaptive responses to cellular injury (Piantadosi, 2008, 180423), depending on intracellular concentrations of CO, heme proteins and molecules which modulate CO binding to heme proteins.

5.1.3.4. Summary

CO is a ubiquitous cell signaling molecule with numerous physiological functions. The endogenous generation and release of CO from heme by HO-1 and HO-2 is tightly controlled, as is any homeostatic process. However, exogenously-applied CO has the capacity to disrupt multiple heme-based signaling pathways due to its nonspecific nature. Only a limited amount of information is available regarding the impact of exogenous CO on tissue and cellular levels of CO and on signaling pathways. However recent animal studies demonstrated increased tissue CO levels and biological responses following exposure to 50 ppm CO. Whether or not environmentally-relevant exposures to CO lead to adverse health effects through altered cell signaling is an open question for which there are no definitive answers at this time. However, experiments demonstrating oxidative/nitrosative stress, inflammation, mitochondrial alterations and endothelial dysfunction at concentrations of CO within one or two orders of magnitude higher than ambient concentrations suggest a potential role for such mechanisms in pathophysiologic responses. Furthermore, prolonged increases in endogenous CO resulting from chronic diseases may provide a basis for the enhanced sensitivity of susceptible populations to CO-mediated health effects such as is seen in individuals with coronary artery disease.

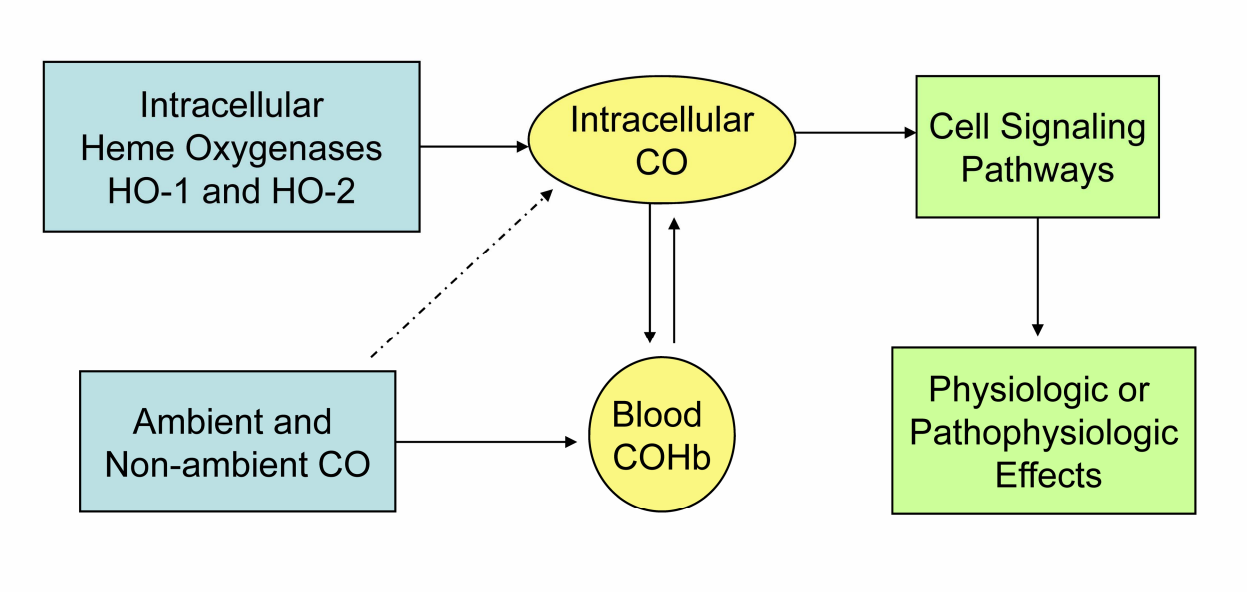


Figure 5-1. Direct effects of CO. The dashed line refers to uptake of inhaled CO by respiratory epithelial cells and resident macrophages in the lung. The uptake of CO by all other cells and tissues is dependent on COHb.

5.2. Cardiovascular Effects

5.2.1. Epidemiologic Studies with Short-Term Exposure

The 2000 CO AQCD (U.S. EPA, 2000, 000907) examined the association between short-term variations in ambient CO concentrations and cardiovascular morbidity. While the results presented by these studies did provide suggestive evidence of ambient CO levels being associated with exacerbation of heart disease, the AQCD determined that the evidence was inconclusive. The reasons

for this conclusion were given as: internal inconsistencies and lack of coherence of the reported results within and across studies; the degree to which average ambient CO levels derived from fixed-site monitors are representative of spatially heterogeneous ambient CO values or of personal exposures that often include nonambient CO; and the lack of biological plausibility for any harmful effects occurring with the very small changes in COHb levels (from near 0 up to 1.0%) over typical baseline levels (about 0.5%) that would be expected with the low average ambient CO concentrations reported in the epidemiologic studies (generally <5.0 ppm, 1-h daily max) (U.S. EPA, 2000, 000907). These reasons were also cited in the discussion of the effects of short-term exposure to CO on mortality and other types of morbidity. The AQCD posited that ambient CO concentrations used as exposure indices in epidemiologic studies may be surrogates for ambient air mixtures produced by combustion sources and/or other constituents of such mixtures. In addition, the AQCD noted that the epidemiologic evidence was stimulating increased scientific interest regarding ambient CO exposures as a potential risk factor for exacerbation of heart disease and other health effects, although the epidemiologic studies were subject to considerable biological and statistical uncertainty.

The following section reviews the literature since the 2000 CO AQCD, including numerous new studies on relevant cardiac endpoints and biomarkers and additional studies of daily hospital admissions for heart disease. New epidemiologic evidence addresses some of the aforementioned uncertainties, including consistency and coherence of results and the possibility that CO may be acting as a surrogate for other combustion-derived air pollutants.

5.2.1.1. Heart Rate and Heart Rate Variability

Heart rate variability (HRV) refers to the beat-to-beat alterations in the heart rate (HR) and is generally determined by analyses of time and frequency domains measured by electrocardiograms (ECG). The time domains often analyzed are (a) normal-to-normal (NN or RR) time interval between each QRS complex, (b) standard deviation of the normal-to-normal interval (SDNN), and (c) mean squared differences of successive difference normal-beat to normal-beat intervals (rMSSD). Shorter time domain variables results in lower HRV. The frequency domains often analyzed are (a) the ratio of low energy frequency (LF) to high energy frequency (HF), and (b) the proportion of interval differences of successive normal-beat intervals greater than 50 ms (PNN_{50}), reflecting autonomic balance. Decreased HRV is associated with a variety of adverse cardiac outcomes such as arrhythmia, myocardial infarction (MI), and heart failure (Deedwania et al., 2005, 195134; De Jong and Randall, 2005, 193996; Huikuri et al., 1999, 184464; Rajendra et al., 2006, 193787).

Three studies investigated the association between ambient air pollution, including CO, and HRV in Boston, MA and reported inconsistent results. The earlier of these studies recruited 21 active residents aged 53-87 yr and performed up to 12 ECG assessments on each subject over a period of 4 mo (summer 1997). Particles (PM_{10}, $PM_{2.5}$) and several gaseous pollutants (O_3, NO_2, and SO_2) were monitored at fixed sites (up to 4.8 mi from the study site), while CO was monitored 0.25 mi from each participant's residence. Lag periods for the preceding 1 h, 4 h, and 24 h before each subject's HRV assessment were analyzed, and results showed that only $PM_{2.5}$ and O_3 were associated with HRV parameters (Gold et al., 2000, 011432).

A similar study by the same group of researchers 2 yr later involved 28 older subjects (aged 61-89 yr) who were living at or near an apartment complex located on the same street as the Harvard School of Public Health. The subjects were seen once a week for up to 12 wk, and HRV parameters (SDNN, r-MSSD, PNN_{50}, LF/HF ratio) were measured for 30 min each session. Data for $PM_{2.5}$, BC, and CO were recorded at the Harvard School of Public Health (<1 km from the residence) while data for NO_2, O_3, and SO_2 were collected from government regulatory monitoring sites. There were moderate correlations between CO and $PM_{2.5}$ (r = 0.61) and between CO and NO_2 (r = 0.55) but not with SO_2 (r = 0.18) or O_3 (r = 0.21). Similarly, $PM_{2.5}$ was associated with HRV, whereas in contrast to the previous study, CO was associated[1] with a negative change in SDNN (% change: -13 [95% CI: -24.06 to -1.88]), r-MSSD (% change: -31.88 [95% CI: -38 to -7.5]), and PNN_{50} (% change: -46.25 [95% CI -103.95 to -9.38] per 0.5 ppm increase in 24-h avg CO concentration) (Schwartz et al., 2005, 074317).

[1] The effect estimates from epidemiologic studies have been standardized to a 1 ppm increase in ambient CO for 1-h max CO concentrations, 0.75 ppm for 8-h max CO concentrations, and 0.5 ppm for 24-h avg CO concentrations throughout this section (text, tables, and figures).

An additional Boston, MA study examined HRV parameters (SDNN, LF, HF, LF/HF ratio) among 603 persons from the Normative Aging Study, a longitudinal study that originally recruited 2,280 men in the greater Boston area during 1963. The cohort members were examined (November 2000-October 2003) and the ECG data were linked to air pollution data for $PM_{2.5}$, particle number concentration, BC, O_3, NO_2, SO_2, and CO. Lagged pollutant effects for a 4-h, 24-h, and 48-h ma were examined. The main pollutant effects were with $PM_{2.5}$ and O_3, while CO was not associated with HRV (Park et al., 2005, 057331).

A study in Mexico City selected 30 subjects from the outpatient clinic at the National Institute of Cardiology and followed them for ~10 h (starting at 9:00 a.m.) (Riojas-Rodriguez et al., 2006, 156913). Each subject was connected to a Holter ECG monitor (e.g., a portable ECG monitor) and also given personal $PM_{2.5}$ and CO monitors. The subjects went about their usual daily activities, and the personal $PM_{2.5}$ and CO data were linked to various ECG parameters (HR, R-R, LF, HF) at various lags. In copollutant models with $PM_{2.5}$, personal CO exposure for the same 5-min period was significantly associated with a decrease in LF and very low energy frequency (VLF) parameters with coefficients equal to -0.024 (95% CI: -0.041 to -0.007) and -0.034 (95% CI: -0.061 to -0.007), respectively, for a 1 ppm increase in 1-h CO concentration.

In an additional study conducted in Mexico City, 34 residents from a nursing home underwent HRV analysis every other day for 3 mo (Holguin et al., 2003, 057326). Exposure assessment for ambient $PM_{2.5}$ was based on data recorded at a monitor on the roof of the nursing home, while exposures to ambient O_3, NO_2, SO_2, and CO were derived from data recorded at a fixed site 3 km from the nursing home. Exposures for the same day and 1-day lags were analyzed, and only O_3 and $PM_{2.5}$ were positively associated with HRV.

Wheeler et al. (2006, 088453) examined 18 individuals with COPD and 12 individuals with recent MI living in Atlanta, GA. Morning ECG readings were collected by a Holter system by a field technician in the subjects' homes. Ambient air pollution exposures for $PM_{2.5}$, O_3, NO_2, SO_2 and CO were derived from data recorded at fixed sites throughout metropolitan Atlanta. Three exposure periods were analyzed: the hour of the ECG reading, 4-h mean, and 24-h mean before the reading. While positive effects were reported for NO_2 and $PM_{2.5}$, no quantitative results were reported for CO.

After reviewing 2,000 patient charts, Dales (2004, 099036) recruited 36 subjects with CAD from the Toronto Western Hospital's noninvasive cardiac diagnostic unit. HR and HRV (SDNN, N-N, HF, LF, HF/LH ratio) were assessed 1 day each week for up to 10 wk by a Holter monitoring system. Personal air sampling for $PM_{2.5}$ and CO was carried out for the same 24-h period while subjects went about their usual daily activities for that period. Stratified results showed that among those not on beta-receptor-blockers, personal CO exposure was positively associated with SDNN ($p = 0.02$). However, in the group taking beta blockers, there was a negative association ($p = 0.06$). Personal exposure to $PM_{2.5}$ was not associated with HRV.

Peters et al. (1999, 011554) examined HR among a sub-sample of the Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) study (n = 2,681) in Augsburg, Germany. Total suspended particles (TSP), SO_2, and CO data were collected from a single monitoring station located in the center of the city and linked to each subject to estimate exposures on the same day and 5 days prior. A 0.5 ppm change in 24-h CO concentration was associated with an increase in HR of approximately 1 beat per minute, whereas CO based on a 5-day exposure had no effect on HR.

Thirty-one subjects with CHF had their pulse rate recorded daily over a 2-mo period, and the correlation between pulse rate and air pollutants was examined (Goldberg et al., 2008, 180380). There was weak evidence for a decrease in pulse rate associated with the lag 1 SO_2 concentration after adjustment for personal and meteorological factors and no evidence for an effect associated with any of the other air pollutants (adjusted mean difference for CO: 0.245 [95% CI -0.209 to 0.700] lag 0-2).

Liao et al (2004, 056590) investigated men and women aged 45-64 yr from the Atherosclerosis Risk in Communities (ARIC) study (Washington County, MD; Forsyth County, NC; and selected suburbs of Minneapolis, MN). The sample sizes were 4,899, 5,431, 6,232, 4,390 and 6,784 for analyses involving PM_{10}, O_3, CO, NO_2, and SO_2, respectively. County-level exposure estimates for 24-h CO were calculated for 1, 2, and 3 days prior to clinical examination. A 0.5 ppm increase in 24-h CO concentration (at lag 1) was associated with an increase in HR (beats/minute) ($\beta = 0.357$, $p < 0.05$). CO was not significantly associated with changes in SDNN.

The Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air (ULTRA) study was carried out in three European cities: Amsterdam, The Netherlands; Erfurt, Germany; and

Helsinki, Finland; a panel of subjects with CAD was followed for 6 mo with biweekly clinical visits, which included an ECG reading to assess HRV (Timonen et al., 2006, 088747). The time-domain measures of HRV (SDNN and rMSSD) were analyzed along with frequency-domain measures, which included power spectrum densities for LF and HF. Exposures to ambient air pollution ($PM_{2.5}$, PM_{10}, NO_2, CO) were derived from data recorded at fixed-monitoring site networks within each city. Correlation coefficients for NO_2 and CO ranged from 0.32 to 0.86 in the three cities. CO was moderately correlated with PM_{10} in Helsinki (r = 0.40), with $PM_{2.5}$ in Amsterdam (r = 0.58), and more highly correlated with PM_{10} in Erfurt (r = 0.77). Various lag periods were examined, including lag 0 (24 h prior to the clinical visit) through a 0- to 2-day avg lag and a 0- to 4-day avg lag. In total there were 1,266 ECG recordings used in the final analyses. In the pooled analyses (e.g., across cities) a 0.5 ppm increase in 24-h CO concentration was associated with a decrease in LF/HF ratio at lag 1-day (β -16.4 [95% CI: -29.9 to -0.3]), and a decrease in SDNN and HF at lag 2-day (β -3.4 [95% CI: -6.1 to -0.4]; β= -17.6 [95% CI: -34.4 to -0.9], respectively). However, the same study reported no effect for CO on BP and HR (Ibald-Mulli et al., 2004, 087415).

A small panel study in Kuopio, Finland, which was designed as the pilot study for the ULTRA study, examined simultaneous ambulatory ECG and personally monitored CO readings among 6 male patients with CAD (Tarkiainen et al., 2003, 053625). The patients were asked to follow their usual daily activities, but data were recorded only three times with 1-wk intervals. The CO exposures were divided into low (≤ 2.7 ppm) and high (>2.7 ppm) and during the high CO exposure r-MSSD increased on average by 2.4 ms; however, there was no effect on RR or SDNN.

A study in Taiwan recruited 83 patients (aged 40-75 yr) from the National Taiwan University Hospital, Taipei, and conducted ambulatory ECG readings using a Holter system (Chan et al., 2005, 088988). Ambient air pollution exposures for PM_{10}, NO_2, SO_2, and CO were derived from 12 fixed-site monitoring stations across Taipei. Lag periods of 1 h to 8 h prior to the ECG reading were analyzed, and only NO_2 was associated with HRV parameters (SDNN and LF); CO was not associated with HRV.

Min et al. (2009, 199514) investigated the effects of CO on cardiac autonomic function by measuring HRV in patients with and without metabolic syndrome. Several criteria were used to classify metabolic syndrome, including waist circumference, triglycerides and cholesterol levels, blood pressure, and fasting glucose level. The group classified as having metabolic syndrome showed significant decreases in SDNN and HF, and those declines were significantly associated with CO exposure with a 1- to 2-day lag. Copollutant models with PM_{10} and NO_2 gave similar results.

In summary, few studies have examined the effect of CO on HR, and while two of the three studies reported a positive association, further research is warranted to corroborate the current results. Similarly, while a larger number of studies have examined the effect of CO on various HRV parameters, mixed results have been reported throughout these studies. Furthermore, with several HRV parameters often examined, there are mixed results across the studies as to the HRV parameters that are positively associated with CO exposure. Table 5-4 presents a summary of the reviewed studies. Due to the heterogeneity of endpoints (see column "cardiac endpoint" in Table 5-4), these studies do not lend themselves to a quantitative meta-analysis or inclusion in a summary figure.

Table 5-4. Summary of studies investigating the effect of CO exposure on HRV parameters.

Study	Location Sample Size	Cardiac Endpoint	Upper CO Concentrations from AQS[a] in ppm	CO Concentrations Reported by Study Authors in ppm	Copollutants
Gold et al. (2000, 011432)	Boston, MA (n = 21)	HR, SDNN, r-MSSD	98th%: 0.80-2.48 99th%: 0.89-2.57 (24 h)t	Mean: 0.47(24 h) Range: 0.12-0.82	PM_{10}, $PM_{2.5}$, O_3, NO_2, SO_2
Schwartz et al. (2005, 074317)	Boston, MA (n = 28)	SDNN, r-MSSD, PNN, LF/HF	98th%: 0.95-2.14 99th%: 0.96-2.60 (24 h)	25th, 50th, 75th percentiles: 0.38, 0.45, 0.54	$PM_{2.5}$, BC, NO_2, O_3
Park et al. (2005, 057331)	Boston, MA (n = 4 97)	SDNN, LF, HF, LF/HF	98th%: 0.92-1.45 99th%: 0.99-1.66 (24 h)	Mean: 0.50 (24 h) Range: 0.13-1.8	$PM_{2.5}$, BC, O_3, NO_2, SO_2
Riojas-Rodriguez et al. (2006, 156913)	Mexico City, Mexico (n = 30)	HF, LF, VLF, HR, R-R	NA	Mean: 2.9 (11 h) Range: 0.1-18	$PM_{2.5}$
Holguin et al. (2003, 057326)	Mexico City, Mexico (n = 34)	HF,LF, LF/HF	NA	Mean: 3.3(24 h) Range: 1.8-4.8	$PM_{2.5}$, O_3, NO_2, SO_2
Wheeler et al. (2006, 088453)	Atlanta, GA (n = 30)	SDNN, r-MSSD, PNN, LF, HF, LF/HF	98th%: 2.8-3.1 99th%: 2.9-3.8 (8 h)	Mean: 362 ppb (4h) 25th, 50th, 75th percentiles: 221.5, 304.3, 398.1	$PM_{2.5}$, O_3, NO_2, SO_2
Dales (2004, 099036)	Toronto, Canada (n = 36)	SDNN, HF, LF, LF/HF, N-N	NA	Mean: 2.4[b] Range: 0.4-16.5	$PM_{2.5}$
Peters et al. (1999, 011554)	Augsburg, Germany (n = 2681)	HR	NA	Mean: 3.6 Range: 1.5-7.1	TSP, SO_2
Goldberg et al. (2008, 180380)	Montreal, Canada (n-31)	Pulse rate	NA	NR; IQR: 1.8 ppm	NO_2, O_3, SO_2, $PM_{2.5}$
Liao et al. (2004, 056590)	Maryland, North Carolina, Minnesota, (n = 4899-6784)	HR, SDNN, LF, HF	98th%: 0.39-2.29 99th%: 0.43-2.66 (24 h)	Mean: 0.65 (24 h)	PM_{10}, O_3, NO_2, SO_2
Timonen et al. (2006, 088747)	Amsterdam, The Netherlands; Erfurt, Germany; Helsinki, Finland (n = 131)	SDNN, HF, LF/HF	NA	Mean: 0.35-0.52 Range: 0.09-2.17	$PM_{2.5}$, PM_{10}, NO_2
Ibald-Mulli et al. (2004, 087415)	Amsterdam, The Netherlands; Erfurt, Germany; Helsinki, Finland (n = 131)	BP, HR	NA	Mean: 0.35-0.52 Range: 0.09-2.17	UFP, PM_{10}, $PM_{2.5}$, NO_2, SO_2
Tarkiainen et al. (2003, 053625)	Kuopio, Finland (n = 6)	PNN, SDNN, r-MSSD	NA	Mean: 4.6 Range: 0.5-27.4	None
Chan et al. (2005, 088988)	Taipei, Taiwan (n = 83)	SDNN, r-MSSD, LF	NA	Mean: 1.1 Range: 0.1-7.7	PM_{10}, NO_2, SO_2
Min et al. (2009, 199514)	South Korea (n=986)	SDNN, HF, LF	NA	Mean: 0.45 Range: 0.10-7.20	PM_{10}, NO_2, SO_2

NA: Not Available
[a] Includes range across individual monitors in study site; AQS data available for U.S. studies only
[b] 95th percentile of 24-h levels

5.2.1.2. ECG Abnormalities Indicating Ischemia

The ST-segment of an ECG represents the period of slow repolarization of the ventricles and ST-segment depression can be associated with adverse cardiac outcomes, including ischemia. Gold et al. (2005, 087558) recruited a panel of 28 older adults living at or near an apartment complex located within 0.5 km of a monitoring site in Boston, MA. Each subject underwent weekly ECGs for 12 wk in summer 1999 with the main outcome of interest being the ST-segment. Air pollution data in the form of $PM_{2.5}$, BC, and CO were collected from a central site within 0.5 km of the residences of the subjects and averaged over various lag periods (1- to 24-h, 12-h, and 24-h ma) before the ECG. The final analyses included 24 subjects with 269 observations, and results showed consistent negative associations of ST-segment change with increased BC with the strongest association with the 5-h lag. CO during the same lag period also showed a negative association with ST-segment change; however, only BC remained significant in multipollutant models.

The most recent study by this group of researchers utilized a repeated-measures study to investigate the associations between ambient air pollution and ST-segment level changes averaged over 30-min periods in patients with coronary artery disease (CAD) (Chuang et al., 2008, 155731).

The authors reported that increases in mean $PM_{2.5}$, BC, NO_2 and SO_2 concentrations predicted depression of 30-min averaged ST-segment levels. No association of ST-segment depression was observed with CO or O_3.

5.2.1.3. Arrhythmia

Cardiac arrhythmia refers to a broad group of conditions where there is irregular electrical activity in the heart. The main types of arrhythmias are fibrillation, tachycardia, and bradycardia, all resulting from dysfunction of the upper (atria) and lower (ventricle) chambers of the heart. Briefly, fibrillation refers to when a chamber of the heart quivers chaotically rather than pumps in an orderly fashion, tachycardia refers to a rapid heart beat (e.g., >100 beats/min), while bradycardia refers to a slow heart beat (e.g., <60 beats/min). A few air pollution panel studies have examined the occurrence of cardiac arrhythmias by analyzing data recorded by implantable cardioverter defibrillators (ICDs) among cardiac patients. The majority of these studies were conducted in North America, with the main outcome investigated being tachycardia. Results of these studies provide little evidence for an association between cardiac arrhythmia and ambient CO.

For example, Dockery and colleagues (2005, 078995) analyzed the relationship between ambient air pollution and the daily incidence of ventricular tachyarrhythmia among 203 patients with ICDs in Boston, MA. An hourly city average for the Boston metropolitan area was calculated for CO, O_3, NO_2, SO_2, SO_4^{2-}, BC, and $PM_{2.5}$. Although positive associations between ventricular arrhythmic episode days were found for all mean pollutant levels on the same day and previous days, none of these associations approached statistical significance. However, when the analyses were stratified by patients who had a previous incidence of ventricular arrhythmia within 3 days or greater than 3 days to the day of interest, a 0.5 ppm increase in 24-h CO concentration was positively associated with incidence of ventricular arrhythmia (OR: 1.68 [95% CI: 1.18-2.41]) among those who had a ventricular arrhythmia within the last 3 days.

A similar study in eastern Massachusetts examined cardiac arrhythmia by analyzing defibrillator discharges precipitated by either ventricular tachycardia or fibrillation among 100 cardiac patients (Peters et al., 2000, 011347). Exposure to ambient CO was estimated for the same day, 1-day, 2-day, 3-day, and a 5-day mean lag period. CO was moderately correlated with PM_{10} ($r = 0.51$) and $PM_{2.5}$ ($r = 0.56$) and more highly correlated with NO_2 ($r = 0.71$). When analyzing patients who had at least one defibrillator discharge ($n = 33$), there was no association with CO. However, when analyzing patients who had at least 10 discharges ($n = 6$), a 0.5 ppm increase in 24-h CO concentration (lag 0-4) was associated with an increased odds of a defibrillator discharge (OR: 1.66 [95% CI: 1.01-2.76]).

In contrast, other air pollution panel studies conducted in St Louis, MO (among 56 subjects) (Rich et al., 2006, 089814), Atlanta, GA (among 518 subjects) (Metzger et al., 2007, 092856), Boston, MA (among 203 subjects) (Rich et al., 2005, 079620), and Vancouver, Canada (Rich et al., 2004, 055631; Vedal et al., 2004, 055630) (among 34 and 50 subjects respectively) did not find an association between short-term changes in ambient CO and occurrence of cardiac arrhythmia in patients with implantable defibrillators. The study in Boston also examined atrial fibrillation episodes among the same group of subjects and did not find an association with ambient CO (Rich et al., 2005, 079620).

An alternative method used to assess the relationship between cardiac arrhythmia and ambient air pollution is to analyze cardiac data recorded via ECG. Two studies have employed this method and reported inconsistent results. A study in Steubenville, OH, which is located in an industrial area, examined weekly ECG data among 32 nonsmoking older adults for 24 wk during summer and fall (Sarnat et al., 2006, 090489). Ambient exposures for up to 5 days prior to the health assessment (based on a 5-day ma) were calculated for $PM_{2.5}$, SO_4^{2-}, elemental carbon (EC), O_3, NO_2, SO_2, and CO from data recorded at one central monitoring site. Increases in ambient CO were not associated with increased odds of having at least one arrhythmia during the study period.

In contrast, a study in Germany examined the relationship between ambient air pollution and the occurrence of supraventricular (atria) and ventricular tachycardia recorded via monthly 24-h ECGs among 57 subjects over a 6-mo period (Berger et al., 2006, 098702). Exposure estimates were calculated for ambient ultrafine particles, $PM_{2.5}$, CO, NO, NO_2, and SO_2 for various lag periods (0-23 h, 24-47 h, 48-71 h, 72-95 h, and 5-day avg) prior to the ECG. Results showed that a 0.5 ppm increase in ambient 24-h CO concentration (lag 0-4 days prior to ECG) was positively associated

with the occurrence of supraventricular tachycardia (OR: 1.36 [95% CI: 1.08-1.74]). However, ambient CO was not associated with ventricular tachycardia.

In summary, the studies that have examined associations between CO and the occurrence of cardiac arrhythmias provided little evidence of a CO effect on cardiac arrhythmias. While most studies analyzed data from ICDs, very few reported significant associations, which is similar to the studies that analyzed ECG data to evaluate cardiac arrhythmias in association with CO exposures. Table 5-5 summarizes the reviewed studies.

Table 5-5. Summary of studies investigating the effect of CO exposure on cardiac arrhythmias.

Study	Location, Sample Size	Cardiac Endpoint	Upper CO Concentrations from AQS[a] in ppm	CO Concentrations Reported by Study Authors in ppm	Copollutants
ARRHYTHMIAS (AMONG PATIENTS WITH ICDS)					
Dockery et al. (2005, 078995)	Boston, MA (n = 203)	Ventricular tachycardia	98th%: 0.89-2.33 99th%: 0.99-2.55 (24 h)	25th, 50th, 75th, 95th, percentiles: 0.53, 0.80, 1.02, 1.37 (2-day)	$PM_{2.5}$, BC, O_3, NO_2, SO_2, SO_4^{2-}
Peters et al. (2000, 011347)	Massachusetts, US (n = 100)	Ventricular fibrillation or tachycardia	98th%: 1.60-2.58 99th%: 1.75-2.71 (24 h)	Mean: 0.58 (24 h) Max: 1.66	$PM_{2.5}$, PM_{10}, BC, O_3, NO_2, SO_2, SO_4^{2-}
Rich et al. (2006, 089814)	Boston, MA (n = 56)	Ventricular arrhythmia	98th%: 0.89-2.33 99th%: 0.99-2.55 (24 h)	25th, 50th, 75th percentiles: 0.4, 0.5, 0.6 (24 h)	$PM_{2.5}$, EC, O_3, NO_2, SO_2
Metzger et al. (2007, 092856)	Atlanta, GA (n = 518)	Ventricular tachycardia	98th%: 5.0 99th%: 5.6 (1 h)	Mean: 1.7 (1 h) Range: 0.1-7.7	PM_{10}, $PM_{2.5}$, O_3, NO_2, SO_2
Rich et al. (2005, 079620)	Boston, MA (n = 203)	Atrial fibrillation	98th%: 0.89-2.33 99th%: 0.99-2.55 (24 h)	25th, 50th, 75th, 95th, percentiles: 0.53, 0.80, 1.02, 1.37 (2-day)	$PM_{2.5}$, BC, O_3, NO_2, SO_2
Rich et al. (2004, 055631)	Vancouver, Canada (n = 34)	ICD discharge due to arrhythmia	NA	Mean: 0.55 (24 h) IQR: 0.16	$PM_{2.5}$, PM_{10}, EC, O_3, NO_2, SO_2, SO_4^{2-}
Vedal et al. (2004, 055630)	Vancouver, Can (n = 50)	ICD discharge due to arrhythmia	NA	Mean: 0.6 (24 h) Range: 0.3-1.6	PM_{10}, O_3, NO_2, SO_2
ARRHYTHMIAS (VIA ECG)					
Sarnat et al. (2006, 090489)	Steubenville, OH (n = 32)	Atrial or ventricular tachycardia	98th%: 1.42 99th%: 1.81 (24 h)	Mean: 0.2 (24 h) Range: 0.1, 1.5	$PM_{2.5}$, O_3, NO_2, SO_2, SO_4^{2-}, EC
Berger et al. (2006, 098702)	Erfurt, Germany (n = 57)	Atrial or ventricular tachycardia	NA	Mean: 0.45 (24 h) Min, Med, Max 0.10, 0.38, 1.68	PM_{10}, $PM_{2.5}$, NO_2, NO, SO_2, UF

NA: Not Available

[a] Includes range across individual monitors in study site; AQS data available for U.S. studies only.

5.2.1.4. Cardiac Arrest

Cardiac arrest refers to the abrupt loss of heart function due to failure of the heart to contract effectively during systole, which can lead to sudden cardiac death if not treated immediately. Very

few studies have investigated the association between ambient CO exposure and the risk of cardiac arrest, and none reported a significant association between increased CO exposure and the occurrence of cardiac arrest.

Two studies (Levy et al., 2001, 017171; Sullivan et al., 2003, 043156) were evaluated that examined the association between ambient CO and cardiac arrest. Both studies were conducted in Seattle, WA, using a case-crossover study design and found no association between short-term exposure to CO and cardiac arrest.

These studies examined air pollution exposures for black smoke particles (BSP), PM_{10}, SO_2, and CO. The correlation coefficient for PM_{10} and CO was 0.8 in both studies. The first of these studies examined paramedic-attended out-of-hospital primary cardiac arrests among 362 cases (1998-1994) in Seattle and King County, WA, whereby lags of 0-5 days were analyzed (Levy et al., 2001, 017171). There was no indication of association between CO and out-of-hospital primary cardiac arrest (RR 0.99 [95% CI: 0.83-1.18]). The second of these studies examined out-of-hospital primary cardiac arrest for a 10-yr period (1985-1994) among subjects within a health organization database (the Group Health Cooperative of Puget Sound), whereby 0- through 2-day lags were analyzed (Sullivan et al., 2003, 043156). The relative risk of primary cardiac arrest was 0.95 (95% CI: 0.85-1.05; lag 0).

5.2.1.5. Myocardial Infarction

As previously stated, MI is commonly referred to as "heart attack" and is another cardiac outcome that has received limited attention within the area of air pollution research. Only one study has investigated the association between short-term changes in ambient CO and the onset of MI. Peters and colleagues (2001, 016546) employed a case-crossover study design to analyze short_term exposures (0-5 h and 0-5 days before the onset of MI) to particles (PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, BC) and gases (CO, O_3, NO_2, SO_2) among 772 patients with MI in the greater Boston area. While all pollutants showed positive associations with the onset of MI, only $PM_{2.5}$ reached statistical significance with the main exposure period (2 h before the onset) (OR for CO: 1.22 [95% CI: 0.89-1.67]).

5.2.1.6. Blood Pressure

Only two studies have investigated whether short-term exposure to CO influences BP. The earlier of these two studies examined BP among 2,607 men and women aged 25-64 yr who participated in the Augsburg, Germany, MONICA study (Ibald-Mulli et al., 2001, 016030). Exposures to ambient TSP, SO_2 and CO (from one monitor in the center of the city) during the same day as the BP reading and an average over the 5 days prior were examined. Results showed that ambient CO had no association with BP.

Similarly, the second of these studies extracted baseline and repeated measures of cardiac rehabilitation data from a Boston, MA, hospital for 62 subjects with 631 visits and analyzed ambient air pollution exposures (with particular focus on $PM_{2.5}$) averaged over various periods up to 5 days before the visit (Zanobetti et al., 2004, 087489). While results showed significant associations between increased BP and ambient $PM_{2.5}$, SO_2, O_3, and BC, there was no significant effect for CO (results not presented quantitatively).

5.2.1.7. Vasomotor Function

Gaseous pollutants, including SO_2, NO and CO, were found to affect large artery endothelial function among 40 healthy white male nonsmokers in Paris, France, whereas PM was found to exaggerate the dilatory response of small arteries to ischemia (Briet et al., 2007, 093049). Changes in amplitude of flow-mediated dilatation were highly dependent on changes in 5-day lag concentrations of SO_2, NO and CO, but not NO_2, $PM_{2.5}$ or PM_{10}. The effect attributed to CO (β coefficient: -0.68 [95% CI: -1.22 to -0.15]) was the smallest in magnitude when compared to those for SO_2 and NO, but overall the effect estimates were similar and all were statistically significant. Similarly, $PM_{2.5}$, PM_{10}, NO_2 and CO were positively correlated with small artery reactive hyperemia, and the effect attributed to CO was the smallest in magnitude when compared to those for $PM_{2.5}$, PM_{10}, and NO_2; but overall, the effect estimates were similar and all were statistically significant.

5.2.1.8. Blood Markers of Coagulation and Inflammation

Several studies have investigated the association between ambient CO and various blood markers related to coagulation and inflammation. The main endpoints analyzed have been plasma fibrinogen, B-type natriuretic peptide (BNP), endothelial function, Factor VII, C-reactive protein (CRP), prothrombin, intercellular adhesion molecule (ICAM-1), and white blood cell count (WBC).

Delfino et al. (2008, 156390) measured blood plasma biomarkers in a panel of 29 nonsmoking, elderly subjects with a history of CAD living in retirement communities in the Los Angeles, CA, air basin, in order to identify associations with systemic inflammation. The blood plasma biomarkers included CRP, fibrinogen, tumor necrosis factor-α (TNF- α) and its soluble receptor-II (sTNF-RII), interleukin-6 (IL-6) and its soluble receptor (IL-6sR), fibrin D-dimer, soluble platelet selectin (sP-selectin), soluble vascular cell adhesion molecule-1 (sVCAM-1), soluble ICAM-1, and myeloperoxidase (MPO). Overall, there were statistically significant associations for many of the biomarker and pollutant combinations, with some of the strongest effects for CRP, IL-6 and sTNF-RII with indoor and outdoor concentrations of NO_2 and CO. Only the outdoor concentrations indicated an effect of PM for these three biomarkers of inflammation. There was weak evidence for an effect of outdoor and indoor CO on the biomarker of platelet activation (sP-selectin), and for an effect of many of the air pollutants examined on fibrinogen, TNF- α, sVCAM-1, sICAM-1, and MPO. Parameter estimates for fibrin D-dimer were close to zero for most models. Overall, the results suggest that traffic related pollutants, including $PM_{2.5}$, UFPs, OC and CO, lead to increases in systemic inflammation and platelet activation in elderly people with a history of CAD.

Delfino et al. (2009, 200844) added a second year of data from 31 additional subjects to data used in their previous analysis of 29 subjects (Delfino et al., 2008, 156390). This updated panel study of 60 elderly individuals with CAD investigated the relationship of air pollutants to changes in circulating biomarkers of inflammation, platelet activation and antioxidant capacity. The updated analysis focused on the biomarkers that were most informative in the previous analysis (Delfino et al., 2008, 156390) and included IL-6, TNF-α, sTNF-RII, CRP, and sP-selectin. Additionally, frozen-thawed erythrocyte lysates were assayed spectrophotometrically for activities of two antioxidant enzymes, glutathione peroxidase-1 (GPx-1) and copper-zinc superoxide dismutase (Cu,Zn-SOD). Hourly outdoor home-air pollutants were measured over 9 days before each blood draw. There was evidence for an association of CO with IL-6, P-selectin, TNF-RII and CRP, but not for TNF- α, Cu,Zn-SOD, or GPx-1. Many positive associations were found for IL-6, sP-selectin, sTNF-RII, TNF- α, and CRP with markers of traffic-related air pollution (EC, OC, BC, NO_X, and CO), confirming the earlier finding that traffic related pollutants may lead to increases in systemic inflammation and platelet activation in elderly people with a history of CAD.

Circulating levels of BNP are directly associated with cardiac hemodynamics and symptom severity in patients with heart failure and serve as a marker of functional status. Wellenius et al. (2007, 092830) examined the association between BNP levels and short-term changes in ambient air pollution levels among 28 patients with chronic stable heart failure and impaired systolic function. The authors reported no association between CO along with the other pollutants examined and measures of BNP at any lag.

Pekkanen et al. (2000, 013250) examined the association between daily concentrations of air pollution and concentrations of plasma fibrinogen measured among 4,982 male and 2,223 female office workers in Whitehall, London, U.K., between September 1991 and May 1993. Plasma fibrinogen data were linked to ambient exposure to BS, PM_{10}, O_3, NO_2, SO_2, and CO, where the exposures were derived from data recorded at 5 fixed sites across London. There was a high correlation between levels of CO and NO_2 ($r = 0.81$) and more moderate correlations of CO with PM_{10} ($r = 0.57$) and SO_2 ($r = 0.61$). The pollution data on the same day when the blood sampling was done (lag 0) and on the 3 previous days (lags 1-3) were analyzed. Results showed that ambient CO at all lags was associated with an increase in plasma fibrinogen. Results were similar for NO_2, while all other pollutants were not associated with an increase in plasma fibrinogen.

Liao et al. (2005, 088677) examined associations between various air pollutants and hemostatic and inflammatory markers (fibrinogen, factor VIII-C, von Willebrand factor, serum albumin, WBC) among 10,208 middle-aged males and females from the ARIC study. Exposure estimates for ambient PM_{10}, NO_2, SO_2, O_3 and CO were calculated for days 1-3 prior to the blood sampling. A 0.5 ppm increment in 24-h CO concentration was significantly associated with 0.015 g/dL decrease in serum albumin among persons with a history of cardiovascular disease (CVD). CO was not associated with other hemostatic or inflammatory factors.

In Israel, Steinvil et al. (2008, 188893) examined WBC, fibrinogen, and CRP among 3,659 study subjects enrolled in the Tel-Aviv Sourasky Medical Center inflammation survey, in which subjects lived <11 km from an ambient air pollution monitor. Air pollution data in the form of PM_{10}, NO_2, SO_2, O_3, and CO were derived from data recorded at fixed sites. The correlation coefficients were high between CO and NO_2 (r = 0.86) and PM_{10} (r = 0.75). Exposures for lag days 0-7 were analyzed, and ambient CO had a negative effect on fibrinogen only among males. Negative associations were reported for lag 0 (e.g., same day) and lags 2-5 with the decrease in fibrinogen ranging from -5.5 mg/dL to -9.8 mg/dL per 0.5 ppm increase in 24-h CO concentration. A similar negative effect for CO was observed on WBC among males only. The average CO exposure over the week prior to the sampling yielded the largest reduction in WBC (-263 cells/μL).

In a German study, Rückerl and colleagues (Ruckerl et al., 2006, 088754) recruited 57 nonsmoking male patients with CHD who were scheduled for 12 subsequent clinical visits where samples of blood were collected. The authors tested the primary hypothesis that CRP would increase in association with a rise in air pollution levels. CRP is an acute phase protein that increases during inflammatory processes in the body. Other markers of inflammation (serum amyloid A [SAA]), cell adhesion (E-selectin, von Willebrand factor antigen [vWF], ICAM-1), and coagulation (fibrinogen, factor VII [FVII], prothrombin fragment 1+2) were also examined. Ambient air pollution in the form of PM_{10}, UFP, EC, NO_2, and CO was monitored at one central site, and a 24-h avg immediately preceding the clinic visit (lag 0) and up to 5 days (lags 1-4) was calculated for each patient. For CRP, the odds of observing concentrations above the 90th percentile (8.5 mg/L) were 2.41 (95% CI: 1.23-5.02) in association with a 0.5 ppm increase in 24-h CO concentration (lag 2). CO concentration during lags 1 and 2 was associated with observing ICAM-1 concentrations above the 90th percentile (OR: 2.41 [95% CI: 1.49-4.04]; OR: 3.17 [95% CI: 1.77-6.11], respectively). CO concentration (lag 0-3) was associated with a decrease in FVII.

A similar study by Rückerl and colleagues (2007, 156931) was conducted among 1,003 MI survivors across six European cities (Athens, Greece; Augsburg, Germany; Barcelona, Spain; Helsinki, Finland; Rome, Italy; Stockholm, Sweden). The study compared repeated measurements of interleukin-6 (IL-6), CRP and fibrinogen with concurrent ambient levels of air pollution (particle number count [PNC], PM_{10}, $PM_{2.5}$, NO, NO_2, O_3, SO_2, CO) from fixed sites across each city. Lags 0-1 and the 5-day mean prior to the blood sampling were analyzed and ambient CO was not associated with any of the inflammatory endpoints.

Baccarelli et al. (2007, 090733) recruited 1,218 healthy individuals from the Lombardia region in Italy and assessed whether blood coagulability is associated with ambient air pollution. The main blood coagulability endpoints of interest were prothrombin time (PT) and activated partial thromboplastin time (APTT), which are measures of the quality of the coagulation pathways, assuming that, if shortened these measures would reflect hypercoagulability. Air pollution data (PM_{10}, O_3, NO_2, and CO) were obtained from 53 fixed stations across the Lombardia region, which was divided into 9 different study areas, and a network average for each pollutant was calculated across the available monitors within each of the 9 study areas. The analyses examined air pollution at the time of the blood sampling, as well as averages for the 7 days prior and 30 days prior. Results showed that ambient CO at the time of blood sampling was associated with a decrease in PT (coefficient = -0.11 [95% CI: -0.18 to -0.05], $p < 0.001$), indicating hypercoagulability. However, PM_{10} and NO_2 at the time of blood sampling were also associated with a decrease in PT and results from multipollutant models were not reported. Acute phase reactants such as fibrinogen and naturally occurring anticoagulants such as antithrombin, protein C and protein S were examined and none were associated with ambient air pollution.

Rudez et al. (2009, 193783) collected 13 consecutive blood samples within a 1-yr period and measured light-transmittance platelet aggregometry, thrombin generation, fibrinogen and CRP in 40 healthy individuals in Rotterdam, The Netherlands. In general, air pollution increased platelet aggregation as well as coagulation activity but had no clear effect on systemic inflammation. Specifically, there were notable associations between maximal aggregation and CO, NO and NO_2 and between late aggregation and CO. The effects for CO were the highest in magnitude and persisted over most of the lag times investigated. There also was evidence of an increase in endogenous thrombin potential and peak thrombin generation associated with CO, NO, NO_2 and O_3, but no clear associations between PM_{10} and peak height or lag time of thrombin generation. In addition, there was no evidence for an effect of any of the air pollutants examined on CRP or fibrinogen levels. These prothrombotic effects may partly explain the relationship between air pollution and the risk of ischemic cardiovascular disease.

Ljungman et al. (2009, 191983) investigated the effect of CO and NO_2 on inflammation in certain genetic subpopulations of MI survivors. Specifically, they examined whether IL-6 and fibrinogen gene variants could affect plasma IL-6 response to CO or NO_2. The study included 955 MI survivors from 6 European cities. This study provides evidence of gene-environment interaction where IL-6 and fibrinogen gene polymorphisms modified the effects of CO and NO_2 on IL-6 levels in this panel of subjects with existing cardiovascular disease. Subjects with the homozygous major allele genotypes for all 3 IL-6 polymorphisms examined showed larger IL-6 responses to increased CO, and there was evidence of a genetic interaction with NO_2 for one of the polymorphisms. Subjects with the homozygote minor allele genotype for one fibrinogen polymorphism showed both a larger and clearer effect modification for the IL-6 response to increased CO compared to the IL-6 polymorphisms. Similar magnitudes of effect modification were seen for NO_2, but the effect modification pattern was not statistically significant. A second fibrinogen polymorphism did not modify the response to air pollution. Overall, this study provides evidence for the influence of CO on IL-6 levels in subjects with genetic polymorphisms of the IL-6 and fibrinogen genes. In this study, 16% of the subjects had a polymorphism combination that resulted in a statistically significant gene-gene-environment interaction potentially implicating a higher risk of health effects from air pollution in these patients with ischemic heart disease.

In summary, a growing number of studies provide some evidence of a link between CO exposure and blood markers of coagulation and inflammation. Further studies are required to determine whether the prothrombotic effects characterized by many of the blood markers may partly explain the relationship between CO and the risk of ischemic cardiovascular disease. The results of a recent gene-gene-environment interaction study are particularly interesting. Table 5-6 summarizes the reviewed studies. Due to the heterogeneity of endpoints (see column "cardiac endpoint" in Table 5-6), these studies do not lend themselves to a quantitative meta-analysis or inclusion in a summary figure.

Table 5-6. Summary of studies investigating the effect of CO exposure on blood markers of coagulation and inflammation.

Study	Location, Sample Size	Cardiac Endpoint	Upper CO Concentrations from AQS[a] in ppm	CO Concentrations Reported by Study Authors in ppm	Copollutants
Delfino et al. (2008, 156390)	Los Angeles, CA (n=29)	CRP, fibrinogen, TNF-α, IL-6, fibrin D-dimer, sP-selectin, sVCAM-1, sICAM-1, MPO	98th%: 2.9 99th%: 3.1 (1 h)	Outdoor Mean: 0.71 (1 h) Indoor Mean: 0.78 (1 h)	O_3, NO_2, EC, OC, BC, $PM_{0.25}$, $PM_{0.25-2.5}$, $PM_{2.5-10}$
Delfino et al. (2009, 200844)	Los Angeles, CA (n=60)	CRP, TNF-α, IL-6, sP-selectin, sTNF-RII, Cu,Zn-SOD, GPx-1	NA	Outdoor mean: 0.50-0.58 (1h)	O_3, NO_2,NO_x, EC, OC, BC, SOC, PN, $PM_{0.25}$, $PM_{0.25-2.5}$, $PM_{2.5-10}$
Wellenius et al. (2007, 092830)	Boston, MA (n=28)	BNP	98th%: 0.75-2.22 99th%: 0.92-2.48 (24 h)	Mean: 0.44 (24 h)	$PM_{2.5}$, SO_2, NO_2, O_3, BC
Pekkanen et al (2000, 013250)	London, U.K. (n = 7205)	Plasma fibrinogen	NA	Mean: 1.22 (24 h) 10th, 50th, 90th, Max: 0.61, 1.04, 2.0, 8.61	PM_{10}, BS, O_3, NO_2, SO_2
Liao et al (2005, 088677)	US (n = 10.208)	Fibrinogen, VII-C, WBC, albumin, vWF	98th%: 0.39-2.29 99th%: 0.43-2.66 (24 h)	Mean: 1.4 (24 h)	PM_{10}, O_3, NO_2, SO_2
Steinvil et al (2008, 188893)	Tel-Aviv, Israel (n = 3659)	CRP, fibrinogen, WBC	NA	Mean: 0.8 25th, 50th, 75th percentiles: 0.7, 0.8, 1.0	PM_{10}, O_3, NO_2, SO_2
Rückerl et al (2006, 088754)	Erfurt, Germany (n = 57)	CRP, SAA, cell adhesions and coagulation	NA	Mean: 0.45 (24 h) Range: 0.10, 1.68	PM_{10}, $PM_{2.5}$, UFP, EC, NO_2
Rückerl et al (2007, 156931)	Six European cities (n = 1003)	IL-6, CRP, fibrinogen	NA	Mean: 0.29-1.48 (24 h)	PM_{10}, $PM_{2.5}$, O_3, NO_2, SO_2
Baccarelli et al (2007, 090733)	Lombardia Region, Italy (n = 1218)	PT, APTT, fibrinogen, anticoagulants	NA	Mean: 1.14-3.11 Max: 5.52-11.43	PM_{10}, O_3, NO_2, SO_2
Rudez et al. (2009, 193783)	Rotterdam, The Netherlands (n=40)	Platelet aggregation, thrombin generation, fibrinogen, CRP	NA	Median: 0.29 (24 h)	PM_{10}, NO, NO_2, O_3
Ljungman et al. (2009, 191983)	Six European cities (n=955)	IL-6 and fibrinogen polymorphisms	NA	Mean: 0.25-1.29 (24 h)	NO_2, PM_{10}, $PM_{2.5}$

NA: Not Available

[a] Includes range across individual monitors in study site; AQS data available for U.S. studies only.

5.2.1.9. Hospital Admissions and Emergency Department Visits

Since the 2000 CO AQCD (U.S. EPA, 2000, 000907) there have been a number of studies that investigated the effect of ambient CO on hospital admissions and ED visits for CVD. Some of these studies have focused solely on one specific CVD outcome, and these studies are discussed first. The subsequent sections provide a discussion of the studies that investigated hospital admissions and ED visits for all CVD outcomes (e.g., nonspecific) or a variety of specific CVD outcomes.

Coronary Heart Disease

Ischemic heart disease (IHD), also known as CHD, is caused by inadequate circulation of the blood to the heart muscle, which is a result of the coronary arteries being blocked by cholesterol deposits or by vasospasm. CHD can lead to sudden episodes such as MI or death, as well as chronic conditions such as angina pectoris (chest pain).

Ischemic Heart Disease

A number of studies have focused directly on hospitalizations for IHD. There is a lot of variation among these studies with regard to methods employed and results reported. It should be noted that within these studies IHD included MI and angina pectoris (ICD-9 codes 410-414; ICD-10 codes 120, 121-123, 124). A multicity time-series study was conducted to estimate the risk of CVD hospitalization associated with short-term CO exposure in 126 U.S. urban counties from 1999-2005 for over 9 million Medicare enrollees 65 yr old and older (Bell et al., 2009, 193780). The analyses yielded positive associations between same-day CO concentration adjusted for NO_2 concentration and increased risk of hospitalization for IHD 1.004 (95% PI: 1.001-1.007). Cause-specific effect estimates were not presented for CO alone (without adjustment for NO_2).

Mann and colleagues (2002, 036723) investigated the modifying effect of secondary diagnosis of arrhythmia and congestive heart failure (CHF) on the relationship between hospital admissions for IHD (ICD-9: 410-414) and ambient air pollutants for the period of 1988-1995 in southern California. There were 54,863 visits analyzed and a 0.75 ppm increase in 8-h max CO concentration was associated with a 2.69% (95% CI: 1.21-4.19) increase in same-day IHD admissions among persons with a secondary diagnosis of CHF, a 2.23% (95% CI: 1.35-3.13) increase among persons with a secondary diagnosis of arrhythmia, and a 1.21% (95% CI: 0.49-1.94) increase among persons without either secondary diagnosis. Of all the pollutants examined (PM_{10}, NO_2, O_3, CO), only NO_2 showed positive effects estimates similar in magnitude to CO. Although no multipollutant models were analyzed, a moderate to high correlation between CO and NO_2 was found across the seven regions ranging from 0.64 to 0.86. This study indicated that people with IHD and underlying CHF and/or arrhythmia represent a potentially susceptible population relative to the effects of ambient air pollution.

By using a time-series approach, ED visits for IHD (ICD-9: 410-414) in Montreal, Canada, (1997-2002) were examined in relation to ambient CO concentrations (lags 0 and 1) (Szyszkowicz, 2007, 193793). A total of 4,979 visits were analyzed, and results showed significant positive effects with a 0.5 ppm increase in 24-h CO concentration (lag 0), resulting in a 14.1% (95% CI: 5.8-20.6) increase in daily ED visits among all patients. Stratified analyses showed that this effect was mostly among male patients (19.8% [95% CI: 9.2-31.6]). NO_2 was the only other pollutant examined, and it too showed significant positive associations with ED visits for IHD for same-day exposure; however, no multipollutant models were examined.

Lee and colleagues (2003, 095552) examined daily counts of hospital admissions for IHD in Seoul, Korea, for the period from December 1997 to December 1999. Single-day lags 0-5 were analyzed, and the lag period with the strongest association for each pollutant was presented by the authors. For CO, lag 5 showed the strongest effect, with a 1 ppm increase in 1-h maximum (max) CO concentration associated with a daily increase in the number of hospital admissions for IHD; however, this was only among patients 64+ yr of age (RR: 1.07 [95% CI: 1.01-1.13]). All other pollutants (PM_{10}, O_3, NO_2) except SO_2 showed similar significant effects and in a copollutant model with PM_{10} the CO effect was somewhat attenuated (RR 1.04 [95% CI: 0.98-1.11]).

Other studies have examined hospital admissions for IHD while investigating a broad group of CVD outcomes. A study was conducted in Atlanta, GA, where over 4 million ED visits from 31 hospitals for the period 1993-2000 were analyzed (Study of Particles and Health in Atlanta [SOPHIA]). Several articles have been published from this research, with two examining cardiovascular admissions in relation to CO concentrations. The first of these (Metzger et al., 2004, 044222) used a time-series design and analyzed a 3-day ma over single-day lags 0-2 as the a priori lag structure. Although of borderline statistical significance, CO was positively associated with an increase in ED visits for IHD (RR 1.016 [95% CI: 0.999-1.034] per 1 ppm increase in 1-h max CO concentration).

The second of these reports (Peel et al., 2007, 090442) examined the association of ambient air pollution levels and cardiovascular-related ED visits with and without specific secondary conditions

(e.g., comorbidity). Within a time-stratified case-crossover design using the same lag structure previously mentioned, the main results showed that a 1 ppm increase in 1-h max CO concentration was associated with an increase in IHD among those without diabetes (OR: 1.023 [95% CI: 1.004-1.042]), and without CHF (OR: 1.024 [95% CI: 1.006-1.042]).

Two Australian studies have also examined associations between ambient CO concentrations and increased hospital admissions for various CVD outcomes. The first of these studies (Barnett et al., 2006, 089770) analyzed data from five of the largest cities in Australia (Brisbane, Canberra, Melbourne, Perth, Sydney) and two New Zealand cities (Auckland, Christchurch) for the period 1998-2001. A time-stratified case-crossover design was employed, and the age groups of 15-64 yr and ≥ 65 yr were analyzed for the 0-1 lag period. The pooled estimates across all cities showed that a 0.75 ppm increase in 8-h max CO concentration was associated with a 1.9% (95% CI: 0.7-3.2) increase in admissions for IHD among the elderly group (≥ 65 yr). No association was observed for the younger age group.

The second of the Australian studies (Jalaludin et al., 2006, 189416) examined ED visits for CVD outcomes in the elderly (65+ yr) in Sydney for the period 1997-2001. Using a time-series approach, single-day lags of 0, 1, 2, 3, and an average over lags 0 and 1 were examined. A 0.75 ppm increase in 8-h max CO concentration (lag 0) was associated with increases in IHD emergency department visits of 3.1% (95% CI: 1.3-4.9).

Angina Pectoris

In the current literature, only one study was identified that focused solely on angina pectoris as an endpoint. Admissions data for angina pectoris were collected from 25 academic hospitals in Tehran, Iran, and linked to ambient air pollution for the period of 1996-2001 (Hosseinpoor et al., 2005, 087413). Using a time-series approach, single-day lags of 0-3 were analyzed and a 0.5 ppm increase in 24-h avg CO concentration at lag 1 was associated with increased hospital admissions for angina (OR: 1.005 [95% CI: 1.003-1.007]). This result persisted in a multipollutant model that also included NO_2, PM_{10}, and O_3 (OR: 1.005 [95% CI: 1.001-1.008]).

Myocardial Infarction

Linn et al. (2000, 002839) examined the association between ambient air pollution and hospital admissions for cardiopulmonary illnesses in metropolitan Los Angeles for the years 1992-1995. Using a time-series approach, a 0.5 ppm increase in same-day 24-h avg CO concentration was associated with a 2.0% increase in MI hospital admissions among people aged >30 yr. When the analyses were stratified by season, no significant effects were observed (no quantitative seasonal effects reported).

A time-series study in Denver, Colorado, investigated daily hospital admissions for various CVD outcomes among older adults (>65 yr) across 11 hospitals (Koken et al., 2003, 049466). Data between July and August for the period 1993-1997 were analyzed. Single-day lags 0-4 were examined and CO showed no association with hospital admissions for MI (quantitative results were not reported).

As part of the Health Effects of Air Pollution among Susceptible Subpopulations (HEAPSS) study, Lanki et al. (2006, 089788) investigated the association between traffic-related exposure to air pollutants and hospitalization for first acute myocardial infarction (AMI). Data were collected from five European cities with either AMI registers (Augsburg, Barcelona) or hospital discharge registers (Helsinki, Rome, Stockholm). Correlation coefficients between CO and NO_2 ranged from 0.43 to 0.75 across the five cities, and between CO and PM_{10} the range was 0.21 to 0.56. A total of 26,854 hospital admissions were analyzed, and pooled estimates from all five cities showed that there was a weak positive association with AMI hospital admissions and 24-h avg CO concentrations at lag 0 (RR: 1.014 [95% CI: 1.000-1.029] per 0.5 ppm increase), but more so when only using data from the three cities (Helsinki, Rome, Stockholm) with hospital discharge registers (RR: 1.020 [95% CI: 1.003-1.035] per 0.5 ppm increase). When analyses were stratified by fatality and age, results showed that the CO effect was significantly associated with fatal AMI among the <75-yr age group (RR: 1.080 [95% CI: 1.017-1.144]) and with non-fatal AMI in the ≥ 75-yr age group (RR: 1.044 [95% CI: 1.011-1.076]).

Further analyses within the HEAPSS cohort were conducted using the event of cardiac readmission among the first MI survivors (n = 22, 006) (Von Klot et al., 2005, 088070). The readmissions of interest were those with primary diagnosis of AMI, angina pectoris, dysrhythmia,

and heart failure that occurred at least 29 days after the index event. Single-day lags 0-3 were examined, and pooled estimates from all 5 cities showed that a 0.5 ppm increase in same-day (lag 0) CO was associated with an increase in cardiac (e.g., any of the diagnoses) readmissions (RR: 1.041 [95% CI: 1.003-1.076]); this persisted in two-pollutant models that included either PM_{10} or O_3. Correlation coefficients with CO ranged from 0.21 to 0.57 for PM_{10} and 0.44 to 0.75 for NO_2.

A study in Rome, Italy, also found an association between ambient CO and hospitalizations for first-episode MI among 6,531 subjects (January 1995-June 1997) (D'Ippoliti et al., 2003, 074311). A case-crossover design with stratification of time into separate months was used to select referent days as the days falling on the same day of the week within the same month as the index day. CO concentration was positively associated with lag 2 (OR: 1.019 [95% CI: 1.001-1.037]). The other pollutants analyzed were NO_2 and TSP, both of which exhibited a significant positive effect at lag 0. TSP also showed a significant positive effect at lag 0-2 and, when entered into a model with CO, the CO effect did not persist.

The previously mentioned Australian and New Zealand study that analyzed data from seven cities (Brisbane, Canberra, Melbourne, Perth, Sydney, Auckland, and Christchurch) for the period 1998-2001 also reported an association between CO and MI hospital admissions (Barnett et al., 2006, 089770). The pooled estimates across all cities showed that a 0.75 ppm increase in 8-h max CO concentration was associated with a 2.4% (95% CI: 0.6-4.1) increase in admissions for MI, but only among older adults (≥ 65 yr). Table 5-7 shows a summary of the CHD hospital admission studies that examined CO exposures.

In summary, the majority of studies reported significant increases in the daily number of admissions for IHD, angina and MI in relation to CO exposures. In studies that stratified by age groups and/or sex, the effects were larger among the elderly and males. Among the different lag periods being examined, the associations were more commonly observed with same day CO (lag 0) or an average over the same day and previous day (lag 0-1). Figure 5-2 shows the effect estimates associated with daily admissions for various forms of CHD from selected studies.

Study	Location	Lag	Age	Group/Outcome	Effect Estimate (95% CI)
Metzger et al. (2004, 044222)	Atlanta, GA	0-2			IHD
Peel et al. (2007, 090442)	Atlanta, GA	0-2			
Mann et al.(2002, 036723)	California, US	0-3			
	California, US	0-3		sCHF	
	California, US	0-3		sARR	
Barnett et al. (2006, 089770)	Australia, New Zealand	0-1	15-64 yr		
	Australia, New Zealand	0-1	65+ yr		
Jalaludin et al. (2006, 189416)	Sydney, Australia	0-1	65+ yr		
Szyszkowicz (2007, 193793)	Montreal, Canada	0	All ages		
	Montreal, Canada	0	All ages	Males	
	Montreal, Canada	0	All ages	Females	
	Montreal, Canada	0	65+ yr	Males and Females	
	Montreal, Canada	0	65+ yr	Males	
	Montreal, Canada	0	65+ yr	Females	
Lee et al. (2003, 095552)	Seoul, Korea	5	All ages		
	Seoul, Korea	5	64+ yr		
von Klot et al. (2005, 088070)	Multicity, Europe	0	35+ yr		Angina
Hosseinpoor et al. (2005, 087413)	Tehran, Iran	1	All ages		
Linn et al. (Linn et al., 2000, 002839)	Los Angeles, CA	0		All year	MI
Barnett et al. (2006, 089770)	Australia, New Zealand	0-1	15-64 yr		
	Australia, New Zealand	0-1	65+ yr		
Lanki et al. (2006, 089788)	Multicity, Europe	0	35+ yr	All cities	
	Multicity, Europe	0	<75 yr	Nonfatal	
	Multicity, Europe	0	<75 yr	Fatal	
	Multicity, Europe	0	75+ yr	Nonfatal	
	Multicity, Europe	0	75+ yr	Fatal	
von Klot et al. (2005, 088070)	Multicity, Europe	0	35+ yr		
D'Ippoliti et al. (2003, 074311)	Rome, Italy	0-2	18+ yr		
	Rome, Italy	0-2	18-64 yr		
	Rome, Italy	0-2	65-74 yr		
	Rome, Italy	0-2	75+ yr		

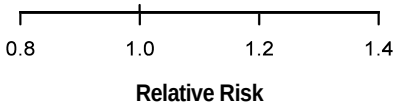


Figure 5-2. Summary of effect estimates (95% confidence intervals) associated with hospital admissions for various forms of CHD. Effect estimates have been standardized to a 1 ppm increase in ambient CO for 1-h max CO concentrations, 0.75 ppm for 8-h max CO concentrations, and 0.5 ppm for 24-h avg CO concentrations.

Table 5-7. Summary of CHD hospital admission studies.[a]

Study	Location	Endpoints Examined	Copollutants	Lags Examined	Upper CO Concentrations from AQS[c] in ppm	CO Concentrations Reported by Study Authors in ppm
STUDIES THAT FOCUSED SOLELY ON CHD						
Mann et al. (2002, 036723)	Southern California (1988-1995)	IHD	PM_{10}, NO_2, O_3	0,1,2, 2-4ma	98th%: 1.0-13.8 99th%: 1.3-15.9 (8 h)	Mean: 2.07 (8h)
Szyszkowicz (2007, 193793)	Montreal, Can (1997-2002)	IHD	NO_2	0,1	NA	Mean: 0.5 (24 h)
Lee et al.(2003, 095552)	Seoul, Korea (1997-1999)	IHD	PM_{10}, NO_2, SO_2, O_3	0,1,2,3,4,5	NA	Mean: 1.8
Lanki et al. (2006, 089788)[b]	5 European cities (1992-2000)	MI (first acute)	PM_{10}, NO_2, O_3, PNC	0,1,2,3	NA	Highest city was Rome. 25th = 1.5 75th = 2.6
von Klot et al. (2005, 088070)[b]	5 European cities (1992-2001)	MI, Angina, Cardiac[a]	PM_{10}, NO_2, O_3, PNC	0,1,2,3	NA	Mean: highest city was Rome: 1.9 (24 h)
D'Ippoliti et al. (2003, 074311)[b]	Rome, Italy (1995-1997)	MI	TSP, NO_2, SO_2	0,1,2,3,4, 0-2	NA	Mean: 3.8 (24 h)
Hosseinpoor et al. (2005, 087413)[b]	Tehran, Iran (1996-2001)	Angina	PM_{10}, NO_2, SO_2, O_3	0,1,2,3	NA	Mean: 9.4 (24 h)
STUDIES THAT EXAMINED CHD AMONG OTHER CVDS						
Metzger et al.(2004, 044222)	Atlanta, GA (1993-2000)	IHD, All CVD, CD, CHF, PVCD	PM_{10}, NO_2, SO_2, O_3	0-2ma	98th%: 5.0-5.1 99th%: 5.5-5.9 (1 h)	Mean: 1.8 (1 h)
Peel et al. (2007, 090442)	Atlanta, GA (1993-2000)	IHD, All CVD, CD, CHF, PVCD	PM_{10}, NO_2, SO_2, O_3	0-2ma	98th%: 5.0-5.1 99th%: 5.5-5.9 (1 h)	Mean: 1.8 (1 h)
Barnett et al. (2006, 089770)	Australia and New Zealand (1998-2001)	IHD, MI, All CVD, CA, Stroke	PM_{10}, NO_2, O_3	Lag 0-1	NA	Mean: (8 h) 0.5- 2.1
Jalaludin et al. (2006, 189416)	Sydney, Australia (1997-2001)	IHD, All CVD, Stroke, Cardiac	PM_{10}, NO_2, SO_2, O_3	0,1,2,3, 0-1	NA	Mean: 0.82 (8 h)
Linn et al. (2000, 002839)	Los Angeles, CA (1992-1995)	MI, All CVD, CHF, CA, OS	PM_{10}, NO_2, O_3	0	98th%: 1.0-7.8 99th%: 1.1-8.3 (24 h)	Mean: (24 h) Winter 1.7, Spring 1.0, Summer 1.2, Fall 2.1
Koken et al.(2003, 049466)	Denver, CO (1993-1997)	MI, CAth, PHD, CD, CHF	PM_{10}, NO_2, SO_2, O_3	0,1,2,3,4	98th%: 1.2-2.0 99th%: 1.3-2.0 (24 h)	Mean: 0.9 ppm (24 h)

[a] Cardiac = AMI, angina, dysrhythmia, or HF; CA = Cardiac arrhythmia; CAth = Cardiac atherosclerosis; CD = cardiac dysrhythmias; CHF = Congestive heart failure; PHD = Pulmonary heart disease; OS = Occlusive stroke; PVCD = peripheral vascular and cerebrovascular disease, ma = moving average.

[b] These studies presented CO concentrations in the units mg/m^3. The concentrations were converted to ppm using the conversion factor 1 ppm = 1.15 mg/m^3, which assumes standard atmosphere and temperature.

[c] Includes range across individual monitors in study site; AQS data available for U.S. studies only.

NA: Not Available

Stroke

A stroke is the result of either the blood supply to the brain being blocked (e.g., embolism), which refers to an ischemic stroke (80% of strokes), or the occurrence of a burst blood vessel or hemorrhaging, referred to as a hemorrhagic stroke. Hemorrhagic stroke has two main groupings; intracerebral hemorrhagic stroke (10% of strokes), which is when a blood vessel in the brain leaks, and subarachnoid hemorrhage (3% of strokes), which is bleeding under the outer membranes of the brain. The third type of stroke is a transient ischemic attack (TIA) or ministroke, which has the same early symptoms as a normal stroke but the symptoms disappear within 24 h, leaving no apparent deficits. A limited number of air pollution studies have investigated hospital admissions for the three main forms of stroke and generally report small, positive associations or no association with ambient CO concentrations measured during lag periods between 0 and 3 days.

In the multicity time-series study conducted by Bell et al. (2009, 193780), the analyses yielded small, positive associations between same-day CO concentration adjusted for NO_2 concentration and increased risk of hospitalization for cerebrovascular outcomes 1.005 (95% PI: 1.002-1.009). Cause-specific effect estimates were not presented for CO alone (without adjustment for NO_2).

A U.S. study across 9 cities investigated hospital admissions for ischemic and hemorrhagic stroke among Medicare beneficiaries aged 65+ yr of age (155,503 ischemic and 19,314 hemorrhagic admissions from the ED) (Wellenius et al., 2005, 088685). Single-day lags 0-2 were examined and based on a pooled estimate, same-day CO (lag 0) was associated with an increase in ischemic stroke admissions of 1.98% (95% CI: 0.86-3.12) per 0.5 ppm increase in 24-h CO concentration), but not hemorrhagic stroke admissions (-1.14%, 95% CI: -3.40 to 1.18). All other pollutants examined (PM_{10}, NO_2, SO_2) were also associated with an increase in ischemic stroke admissions but not hemorrhagic stroke admissions.

Villeneuve and colleagues (2006, 090191) studied ED visits for hemorrhagic strokes, acute ischemic strokes and transient ischemic attacks among individuals 65+ yr of age at 5 hospitals within the Edmonton, Canada, area between April 1992 and March 2002 (12,422 visits). Within a time-stratified case-crossover design, the analyses were stratified by two seasonal groups (October-March and April-September). CO was found to only have an effect on ischemic stroke during April-September (OR: 1.32 [95% CI 1.09-1.60] per a 0.5 ppm increase in 24-h CO concentration) for a 3-day avg across lags 0-2. CO had no effect on any other stroke subtype. In two-pollutant models the CO effect on ischemic stroke persisted after controlling for PM_{10}, $PM_{2.5}$, SO_2, and O_3.

In Kaohsiung City, Taiwan, CO averaged over lags 0-2 was associated with increased admissions for stroke across 63 hospitals (Tsai et al., 2003, 080133). From 1997 through 2000 a total of 23,179 admissions were analyzed, and on warm days ($\geq$ 20°C) the odds ratios for primary intracerebral hemorrhage and ischemic stroke were 1.39 (95% CI: 1.16-1.66) and 1.39 (95% CI: 1.25-1.53) respectively for a 0.5 ppm increase in 24-h CO concentration. For the same increase in CO on cool days (<20°C) the odds ratios were 1.33 (95% CI: 0.38-2.55) for intracerebral hemorrhage and 2.68 (95% CI: 1.59-4.49) for ischemic stroke. These results persisted in two-pollutant models that included PM_{10}, SO_2, and O_3 but did not persist when controlling for NO_2.

Earlier research conducted in metropolitan Los Angeles examined hospital admissions for cardiopulmonary illnesses from 1992-1995 (Linn et al., 2000, 002839). Using a time-series approach, a 0.5 ppm increase in 24-h CO concentration (lag 0) was associated with a 2.18% (95% CI: 1.73-2.62) increase in occlusive (ischemic) stroke hospital admissions among people aged >30 yr. When the analyses were stratified by season, there was a 1.8% (p=0.017) increase during winter, a 4.55% (p=0.039) increase during summer, and a 1.6% (p=0.015) increase during fall (results for spring were not reported).

A study in Taipei, Taiwan, analyzed 8,582 emergency admissions for cerebrovascular diseases, hemorrhagic stroke, ischemic stroke, and all strokes during 1997-2002 (Chan et al., 2006, 090193). Single-day lags 0-3 were analyzed, and a 0.75 ppm increase in 8-h max CO concentration (lag 2) was associated with an increase in cerebrovascular diseases (OR: 1.03 [95% CI: 1.01-1.05]) and all strokes (OR: 1.03 [95% CI: 1.01-1.05]). These results persisted in two- and three-pollutant models that included O_3 and PM_{10}. There was no association with individual ischemic or hemorrhagic stroke. CO was moderately correlated with PM_{10} (r = 0.47) and $PM_{2.5}$ (r = 0.44), and the correlation was higher with NO_2 (r = 0.77).

A time-series study that focused specifically on stroke hospital admissions conducted in Dijon, France, did not report a significant association with ambient CO (Henrotin et al., 2007, 093270). Hospital admissions for different types of first-ever stroke (e.g., ischemic, hemorrhagic) among

subjects >40 yr were analyzed for the period 1994-2004. A bidirectional case-crossover study design was employed where single-day lags between 0-3 days were examined and CO had no significant association for any lag. This was also the case when the analyses were stratified by gender and types of ischemic stroke (large arteries, lacunar, cardioembolic, transient). Of all pollutants examined (PM_{10}, NO_X, O_3, SO_2, CO), only O_3 showed a significant effect.

Two Australian studies examined associations between ambient CO and hospital admissions for various CVDs. The first of these studies analyzed data from five of the largest cities in Australia (Brisbane, Canberra, Melbourne, Perth, Sydney) and two New Zealand cities (Auckland, Christchurch) for the period 1998-2001 (Barnett et al., 2006, 089770). A time-stratified case-crossover design was employed and the age groups of 15-64 yr and ≥ 65 yr were analyzed for the 0-1 lag period (average over lag 0 and 1). The pooled estimates across all cities showed that CO had no effect on stroke admissions (quantitative results not reported).

The second of the Australian studies examined ED visits for CVDs in older adults (65+ yr) in Sydney for the period 1997-2001 (Jalaludin et al., 2006, 189416). Using a time-series approach, single-day lags of 0-3 and an average over lags 0 and 1 (e.g., lag 0-1) were examined, and CO showed no effect on stroke ED visits. When the analyses were stratified by cool and warm periods, a 0.75 ppm increase in 8-h max CO concentration during the cool period was associated with a 3.8% (95% CI: 0.76-6.94) increase in stroke ED visits.

In summary, there was limited evidence that increased ambient CO concentrations might be associated with hospital admissions for stroke. The largest positive effects came from the Taiwan study in Kaohsiung (Tsai et al., 2003, 080133), with slightly larger effects during the warmer period (>20°C). Similarly, in the Canadian study by Villeneuve and colleagues (2006, 090191), there was a stronger effect during the warmer period (April-September). Studies in France and Australia reported no association between ambient CO concentrations and increased hospital admissions or ED visits for stroke. Figure 5-3 shows the effect estimates associated with daily admissions for stroke from selected studies; Table 5-8 shows a summary of the stroke hospital admission studies that examined CO exposures.

Study	Location	Lag	Outcome/Group	Effect Estimate (95% CI)
Wellenius et al. (2005, 088685)	Multicity, US	0-2	65+ yr	Ischemic Stroke
Villeneuve et al. (2006, 090191)	Edmonton, Can	0-2	IS, 65+ yr, All Seasons	
Villeneuve et al. (2006, 090191)	Edmonton, Can	0-2	IS, 65+ yr, Apr-Sep	
Villeneuve et al. (2006, 090191)	Edmonton, Can	0-2	IS. 65+ yr, Oct-Mar	
Villeneuve et al. (2006, 090191)	Edmonton, Can	0-2	CIS, 65+ yr, All Seasons	
Villeneuve et al. (2006, 090191)	Edmonton, Can	0-2	CIS, 65+ yr, Apr-Sep	
Villeneuve et al. (2006, 090191)	Edmonton, Can	0-2	CIS. 65+ yr, Oct-Mar	
Tsai et al. (2003, 080133)	Kaohsiung, Taiwan	0-2	<20°C Temp	
Tsai et al. (2003, 080133)	Kaohsiung, Taiwan	0-2	>20°C Temp	
Linn et al. (2000, 002839)	Los Angeles, CA	0		
Chan et al. (2006, 090193)	Taipei, Taiwan	1		
Henrotin et al. (2007, 093270)	Dijon, France	3		
Wellenius et al. (2005, 088685)	Multicity, US	0-2	65+ yr	Hemorrhagic Stroke
Villeneuve et al. (2006, 090191)	Edmonton, Can	0-2	65+ yr, All Seasons	
Villeneuve et al. (2006, 090191)	Edmonton, Can	0-2	65+ yr, Apr-Sep	
Villeneuve et al. (2006, 090191)	Edmonton, Can	0-2	65+ yr Oct-Mar	
Tsai et al. (2003, 080133)	Kaohsiung, Taiwan	0-2	<20°C Temp	
Tsai et al. (2003, 080133)	Kaohsiung, Taiwan	0-2	>20°C Temp	
Chan et al. (2006, 090193)	Taipei, Taiwan	1		
Henrotin et al. (2007, 093270)	Dijon, France	1		
Chan et al. (2006, 090193)	Taipei, Taiwan	2		Stroke (nonspecific)
Jalaludin et al. (2006, 189416)	Sydney, Australia	0-1		

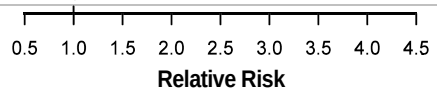


Figure 5-3. Summary of effect estimates (95% confidence intervals) associated with ED visits and hospital admissions for stroke. Effect estimates have been standardized to a 1 ppm increase in ambient CO for 1-h max CO concentrations, 0.75 ppm for 8-h max CO concentrations, and 0.5 ppm for 24-h avg CO concentrations. IS=ischemic stroke, CIS=cerebral ischemic stroke.

Table 5-8. Summary of stroke hospital admission studies.[a]

Study	Location	Type Of Stroke Examined	Copollutants	Lags Examined	Upper CO Concentrations from AQS[c] in ppm	CO Concentrations Reported by Study Authors in ppm
STUDIES THAT FOCUSED SOLELY ON STROKE						
Wellenius et al. (2005, 088685)	9 US cities (1993-1999)	Isch, Hem	PM_{10}, NO_2, SO_2	0,1, 2	98th%: 0.9-5.9 99th%: 1.2-7.1 (24 h)	25th, 50th, 75th percentiles: 0.73, 1.02, 1.44
Villeneuve et al. (2006, 090191)	Edmonton, Can (1992-2002)	Isch, Hem, TIA	NO_2, SO_2, O_3	0,1, 0-2	NA	Mean: 0.8 (24 h)
Tsai et al. (2003, 080133)	Kaohsiung, Taiwan (1997-2000)	Isch, Hem	PM_{10}, NO_2, SO_2, O_3	0-2	NA	Mean: 0.79 (24 h)
Chan et al. (2006, 090193)	Taipei, Taiwan (1997-2002)	All, Isch, Hem	PM_{10}, NO_2, SO_2, O_3	0,1,2,3	NA	Mean: 1.7 (8h)
Henrotin et al. (2007, 093270)[b]	Dijon, France (1994-2004)	Isch, Hem	PM_{10}, NO_X, SO_2, O_3	0,1,2,3	NA	Mean: 0.59 (24 h)
STUDIES THAT EXAMINED STROKE AMONG OTHER CVDS						
Linn et al. (2000, 002839)	Los Angeles, CA (1992-1995)	Isch	PM_{10}, NO_2, O_3	Lag 0	98th%: 1.0-7.8 99th%: 1.1-8.3 (24 h)	Mean: (24 h) Winter 1.7, Spring 1.0, Summer 1.2, Fall 2.1
Barnett et al. (2006, 089770)	Australia and New Zealand (1998-2001)	All	PM_{10}, NO_2, O_3	Lag 0-1	NA	Mean: (8h) 0.5-2.1
Jalaludin et al. (2006, 189416)	Sydney, Australia (1997-2001)	All	PM_{10}, NO_2, SO_2, O_3	0,1,2,3, 0-1	NA	Mean: 0.82 (8h)

[a] Isch = Ischemic; Hem = Hemorrhagic; TIA = transient ischemic attack
[b] These studies presented CO concentrations in the units mg/m^3. The concentrations were converted to ppm using the conversion factor 1 ppm = 1.15 mg/m^3, which assumes standard atmosphere and temperature.
[c] Includes range across individual monitors in study site; AQS data available for U.S. studies only.
NA: Not Available

Congestive Heart Failure

Heart failure (HF) is a condition in which the heart is unable to adequately pump blood to the rest of the body. It does not refer to the cessation of the heart but more to the inability of the heart to operate at an optimal capacity. HF is often called congestive heart failure (CHF), which refers to when the inadequate pumping leads to a buildup of fluid in the tissues. The underlying causes of CHF are hypertension, CAD, MI, and diabetes.

In the multicity time-series study conducted by Bell et al. (2009, 193780), the analyses yielded positive associations between same-day CO concentration adjusted for NO_2 concentration and increased risk of hospitalization for HF (1.009 [95% PI: 1.005-1.012]). Cause-specific effect estimates were not presented for CO alone (without adjustment for NO_2).

Wellenius and colleagues (2005, 087483) examined the rate of hospitalization for CHF among 55,019 Medicare recipients (≥ 65 yr) residing in Allegheny County, PA, during 1987-1999. A time-stratified case-crossover design was employed and single-day lags of 0-3 were analyzed. A 0.5 ppm increase in 24-h avg CO concentration on the same-day (lag 0) was associated with a 4.1% (95% CI: 3.0-5.3) increase in the rate of hospitalization for CHF. This result persisted in copollutant models that included PM_{10}, NO_2, O_3, and SO_2. CO was moderately correlated with SO_2 ($r = 0.54$) and PM_{10} ($r = 0.57$) and more highly correlated with NO_2 ($r = 0.70$).

Another U.S. study recruited 125 patients diagnosed with CHF who were admitted to Johns Hopkins Bayview Medical Center in Baltimore, MD (Symons et al., 2006, 091258). The patients were interviewed after admission through the ED during their stays in overnight wards. The

interview was designed to collect information about symptom onset, health conditions, and factors related to air pollution exposure. Various lag periods (single day and cumulative days 0-3) prior to the onset of symptoms were analyzed and although the focus of this study was exposure to $PM_{2.5}$, of all the pollutants examined ($PM_{2.5}$, CO, NO_2, O_3) only 8-h max CO concentration at lag 2 was significantly associated with the onset of CHF symptoms (OR: 1.68 [95% CI: 1.28-2.80]).

Earlier research conducted in metropolitan Los Angeles, CA examined hospital admissions for cardiopulmonary illnesses (1992-1995) (Linn et al., 2000, 002839). Using a time-series approach, a 0.5 ppm increase in same-day 24-h avg CO concentration was associated with a 1.25% increase in CHF hospital admissions among people >30 yr. When the analyses were stratified by seasons, only summer showed a significant increase (3.7%); however, the study did not report the results for the other seasons.

A time-series study in Denver, CO, investigated daily admissions for various CVDs among older adults (>65 yr) across 11 hospitals (Koken et al., 2003, 049466). Single-day lags 0-4 were examined, and an increase of 0.5 ppm in 24-h avg CO concentration for lag 3 was associated with an 18% (95% CI: 0.2-39.3) increase in risk of hospitalization for CHF.

As stated earlier, a study was conducted in Atlanta, GA, where over 4 million ED visits from 31 hospitals for the period 1993-2000 were analyzed (Metzger et al., 2004, 044222). A time-series design was used and a 3-day ma over single-day lags 0-2 as the a priori lag structure was analyzed. Results showed that 1-h max CO concentration was not associated with an increase in ED visits for CHF (RR: 1.010 [95% CI: 0.988-1.032] per 1 ppm increase). Peel et al. (2007, 090442) examined the same cardiovascular-related effects among those with and without specific secondary conditions (e.g., comorbidity) and found that 1-h max CO concentration was associated with an increase in ED visits for CHF only among those with COPD (OR: 1.058 [95% CI: 1.003-1.115] per 1 ppm increase).

In Kaohsiung city, Taiwan, a study analyzed 13,475 admissions for CHF across 63 hospitals for the period 1996 through 2004 (Lee et al., 2007, 090707). A 0.5 ppm increase in 24-h avg CO concentration averaged over lag days 0-2 was positively associated with CHF hospital admissions on cool days (<25°C) (OR: 1.70 [95% CI: 1.43-2.01]), with a slightly weaker effect on warm days (>25˚ C) (OR: 1.32 [95% CI: 1.15-1.55]). These results persisted in two-pollutant models that included PM_{10}, SO_2, O_3, and models with NO_2 only on warmer days, not with NO_2 on cooler days.

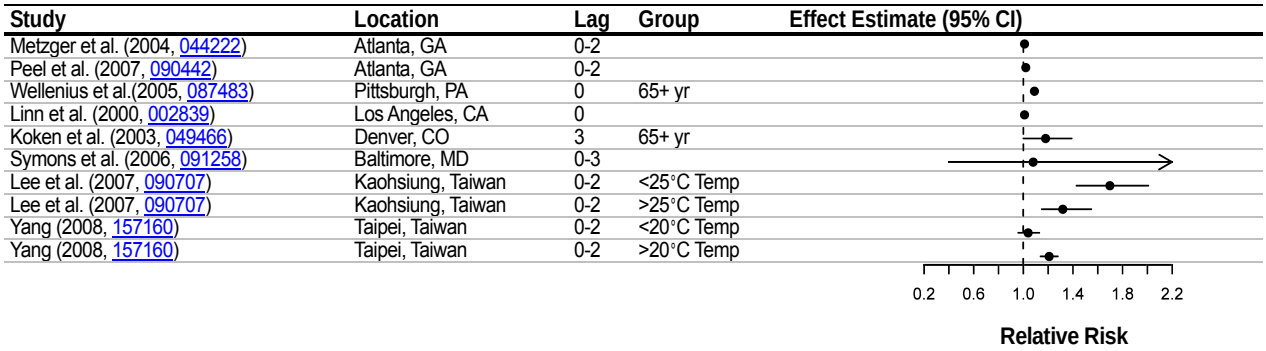


Figure 5-4. Summary of effect estimates (95% confidence intervals) associated with hospital admissions for CHF. Effect estimates have been standardized to a 1 ppm increase in ambient CO for 1-h max CO concentrations, 0.75 ppm for 8-h max CO concentrations, and 0.5 ppm for 24-h avg CO concentrations.

A case-crossover analysis was undertaken to examine the association between levels of ambient air pollutants and hospital admissions for CHF among individuals residing in Taipei, Taiwan, from 1996 through 2004 (Yang, 2008, 157160). During the 9 yr of the study, there were 24,240 CHF hospital admissions for the 47 hospitals in Taipei. The analyses were stratified by temperature, either warm days (>20°C; n = 2325 days) or cool days (<20°C; n = 963 days). The number of CHF admissions was associated with concentrations of PM_{10}, NO_2, CO and O_3 on warm days, however on cool days, the positive effects on increased CHF admissions remained positive, although the effects were diminished for NO_2 and CO, and disappeared completely for PM_{10} and O_3 concentrations. In two-pollutant models, CO remained statistically significant after the inclusion of PM_{10}, SO_2 or O_3 on warm days. On cool days, the effects associated with CO remained positive, but

were no longer statistically significant after the inclusion of PM_{10}, SO_2, or NO_2, but became statistically significant and negative after the inclusion of O_3 in the model (Figure 5-6).

Figure 5-4 shows the effect estimates for associations between CO and daily admissions for CHF from selected studies; Table 5-9 summarizes the CHF hospital admission studies that examined CO exposures.

In summary, many of the studies that examined associations between ambient CO concentrations and daily hospital admissions for CHF reported positive associations at lags of 0-3 days.

Table 5-9. Summary of CHF hospital admission studies.

Study	Location	Endpoints Examined	Copollutants	Lags Examined	Upper CO Concentrations from AQS[a] in ppm	CO Concentrations Reported by Study Authors in ppm
STUDIES THAT FOCUSED SOLELY ON HF						
Wellenius et al. (2005, 087483)	Pittsburgh, PA (1987-1999)	CHF	PM_{10}, NO_2, SO_2, O_3	0,1,2,3	98th%: 1.4-3.4 99th%: 1.6-3.9 (24 h)	Mean: 1.03 (24 h)
Symons et al.(2006, 091258)	Baltimore, MD (2002)	CHF	$PM_{2.5}$, NO_2, O_3	0,1,2,3	98th%: 1.9-2.1 99th%: 2.3 (8 h)	Mean: 0.4 (8 h)
Lee et al. (2007, 090707)	Kaohsiung, Taiwan (1996-2004)	CHF	PM_{10}, NO_2, SO_2, O_3	0-2	NA	Mean: 0.76 (24 h)
Yang (2008, 157160)	Taipei, Taiwan (1996-2004)	CHF	PM_{10}, NO_2, SO_2, O_3	0-2	NA	Mean: 1.26 (24 h)
STUDIES THAT EXAMINED HF AMONG OTHER CVDS						
Linn et al. (2000, 002839)	Los Angeles, CA (1992-1995)	CHF, MI, All CVD, CA, OS	PM_{10}, NO_2, O_3	0	98th%: 1.0-7.8 99th%: 1.1-8.3 (24 h)	Mean: (24 h) Winter 1.7; Spring 1.0 Summer 1.2; Fall 2.1
Koken et al. (2003, 049466)	Denver, CO (1993-1997)	CHF, MI, CAth, PHD, CD	PM_{10}, NO_2, SO_2, O_3	0,1,2,3	98th%: 1.2-2.0 99th%: 1.3-2.0 (24 h)	Mean: 0.9 (24 h)
Metzger et al. (2004, 044222)	Atlanta, GA (1993-2000)	CHF, IHD, All CVD, CD, PVCD	PM_{10}, NO_2, SO_2, O_3	0-2ma	98th%: 5.0-5.1 99th%: 5.5-5.9 (1 h)	Mean 1.8 (1 h)
Peel et al. (2007, 090442)	Atlanta, GA (1993-2000)	CHF, IHD, All CVD, CD, PVCD	PM_{10}, NO_2, SO_2, O_3	0-2ma	98th%: 5.0-5.1 99th%: 5.5-5.9 (1 h)	Mean 1.8 (1 h)

Cardiac = AMI, angina, dysrhythmia, or HF; CA = Cardiac arrhythmia; CAth = Cardiac atherosclerosis; CD = cardiac dysrhythmias; CHF = Congestive heart failure; PHD = Pulmonary heart disease; OS = Occlusive stroke; PVCD = peripheral vascular and cerebrovascular disease, ma = moving average.
NA: Not Available
[a] Includes range across individual monitors in study site; AQS data available for U.S. studies only.

Cardiovascular Diseases

The following section reviews studies that have investigated the effect of CO on ED visits and hospital admissions for all CVD outcomes (e.g., nonspecific). Several of these studies also examined specific CVDs and were briefly discussed in previous sections.

A multicity time-series study was conducted to estimate the risk of CVD hospitalization associated with short-term CO exposure in 126 U.S. urban counties from 1999-2005 for over 9 million Medicare enrollees 65 yr old and older (Bell et al., 2009, 193780). The analyses yielded positive associations between same-day CO concentration and increased risk of hospitalization for total CVD outcomes, which remained positive and statistically significant but were attenuated with copollutant adjustment, especially with NO_2 (Figure 5-6). Overall, a 1 ppm increase in same-day 1-h max CO was associated with a 1.010 (95% PI: 1.008-1.011) increase in risk of CVD admissions.

After adjustment for NO_2, the estimate was attenuated to 1.005 (95% PI: 1.004-1.007). For most cause-specific CVD hospitalizations, associations were positive and statistically significant for same day CO concentration adjusted for same-day NO_2 (IHD 1.004 [95% PI: 1.001-1.007], heart rhythm 1.006 [95% PI: 1.001-1.011], HF 1.009 [95% PI: 1.005-1.012], and cerebrovascular 1.005 [95% PI: 1.002-1.009]). Cause-specific effect estimates were not presented for CO alone (without adjustment for NO_2).

As discussed earlier, a study was conducted in Atlanta, GA where over 4 million ED visits from 31 hospitals for the period 1993-2000 were analyzed (SOPHIA). Several articles have been published from this research, with three examining cardiovascular admissions in relation to CO exposures. The first of these used a time-series design and analyzed a 3-day ma over single-day lags 0-2 as the a priori lag structure (Metzger et al., 2004, 044222). Results showed that a 1 ppm increase in 1-h max CO concentration was associated with an increase in daily ED visits for all CVDs (RR: 1.017 [95% CI: 1.008-1.027]). This persisted in two-pollutant models that included NO_2 and $PM_{2.5}$.

The second of these publications examined the association of ambient air pollution levels and cardiovascular morbidity in visits with and without specific secondary conditions (Peel et al., 2007, 090442). Within a time-stratified case-crossover design, a 3-day ma over single-day lags 0-2 was used as the a priori lag structure. Results from the case-crossover analyses on all cardiovascular and peripheral vascular and cerebrovascular disease were similar to the time-series results presented earlier. Results from the various comorbidity analyses are presented in Table 5-10. Similar to the results from the earlier publication, CO was mostly associated with peripheral vascular and cerebrovascular disease (PVCD) among those with and without comorbidities, except among those with CHF. Overall, there is limited, if any, evidence of susceptibility to the effects of CO concentration for those with comorbid conditions.

Table 5-10. Association of ambient air pollution levels and cardiovascular morbidity in visits with and without specific secondary conditions.

Co-morbidity	IHD	Dysrhythmias	PVCD	CHF
HYPERTENSION				
- With	1.007 (0.978-1.037)	1.065 (1.015-1.118)	1.038 (1.004-1.074)	1.037 (0.997-1.079)
- Without	1.022 (1.000-1.043)	1.008 (0.988-1.029)	1.027 (1.002-1.054)	1.010 (0.985-1.037)
DIABETES				
- With	0.985 (0.945-1.027)	1.058 (0.976-1.146)	1.065 (1.012-1.121)	1.020 (0.975-1.067)
- Without	1.023 (1.004-1.042)	1.014 (0.995-1.034)	1.025 (1.003-1.048)	1.018 (0.993-1.044)
COPD				
- With	0.996 (0.938-1.057)	0.972 (0.878-1.077)	1.113 (1.027-1.205)	1.058 (1.003-1.115)
- Without	1.018 (1.000-1.036)	1.018 (0.999-1.038)	1.026 (1.004-1.047)	1.011 (0.987-1.036)
CHF				
- With	0.956 (0.907-1.007)	1.065 (0.968-1.173)	1.072 (0.981-1.172)	-
- Without	1.024 (1.006-1.042)	1.015 (0.996-1.034)	1.029 (1.008-1.051)	-
DYSRHYTHMIAS				
- With	1.028 (0.985-1.072)	-	1.072 (1.011-1.138)	1.004 (0.960-1.051)
- Without	1.014 (0.995-1.033)	-	1.026 (1.004-1.048)	1.023 (0.998-1.049)

PVCD - peripheral vascular and cerebrovascular disease, IHD = ischemic heart disease, CHF = congestive heart failure.

Source: Reprinted with Permission of Oxford Journals from Peel et al. (2007, 090442)

The third study utilizing the SOPHIA data extended the time period to include 1993 through 2004 (Tolbert et al., 2007, 090316) and focused on two large outcome groups: a respiratory diseases group and a cardiovascular diseases group. The combined cardiovascular case group included the

following groups of primary ICD-9 diagnostic codes: IHD (410-414), cardiac dysrhythmias (427), CHF (428), and peripheral vascular and cerebrovascular disease (433-437, 440, 443-445, 451-453). Results showed that a 1 ppm increase in 1-h max CO concentration was associated with an increase in daily ED visits for all CVDs (RR: 1.016 [95% CI: 1.008-1.024]). CO was the strongest predictor of CVD effects in models with two-pollutant combinations of NO_2, CO and total carbon, as well as in a model including all three pollutants.

Earlier research conducted in Los Angeles, CA, showed that a 0.5 ppm increase in same-day 24-h avg CO concentration was associated with a 1.6% increase in CVD hospital admissions among people >30 yr (Linn et al., 2000, 002839). When the analyses were stratified by season, the strongest CO effect occurred during the winter (1.9% increase) followed by the summer (1.8%) and fall (1.4%) with no effect in spring.

In contrast to other North American studies, a study in Spokane, WA, did not find an association between CO (lags of 1-3 days) and an increase in the number of daily cardiac hospital admissions (quantitative results not reported) (Slaughter et al., 2005, 073854). Similarly, a time-series study in Windsor, Ontario, did not find an association between ambient CO and daily hospital admissions for CVDs (defined as HF, IHD, or dysrhythmias) (Fung et al., 2005, 074322). A total of 11,632 cardiac admissions were analyzed for the period 1995-2000. The lag periods analyzed in this study were lag 0 (same-day), a 2-day avg (lag 0-1), and a 3-day avg (lag 0-2). For a 1 ppm increase in 1-h max CO concentration the mean percent change in daily admissions for the <65-yr age group (lag 0) was -2.6 (95% CI: -6.2 to 3.3); and for the 65+ yr age group, 0.4 (95% CI: -1.9 to 2.7). The authors reported moderate to low correlations with NO_2 (r = 0.38), PM_{10} (r = 0.21) and SO_2 (r = 0.16).

Two case-crossover studies in Taiwan reported an association between ambient CO and hospital admissions for CVDs. In Taipei, a total of 74,509 CVD admissions from 47 hospitals for the period 1997-2001 were analyzed (Chang et al., 2005, 080086). An increase of 0.5 ppm in 24-h avg CO concentration (average over lags 0-2) during warmer periods (≥ 20°C) was associated with an increase in daily hospital admissions (OR: 1.09 [95% CI: 1.065-1.121]) but not cooler periods (<20°C) (OR: 0.98 [95% CI: 0.93-1.004]). These results persisted after controlling for PM_{10}, SO_2, or O_3 in two-pollutant models. An identical study in Kaohsiung analyzed 29,661 CVD admissions for the period 1997-2000 (Yang et al., 2004, 094376). Results showed that a 0.5 ppm increase in 24-h avg CO concentration was associated with an increase in CVD hospital admissions during both the warmer periods (OR: 1.50 [95% CI: 1.38-1.63]) and cooler periods (OR: 1.89 [95% CI: 1.69-2.12]).

Similarly, two Australian studies also reported associations between ambient CO concentrations and increased CVD hospital admissions among older adults. The first of these studies analyzed data from five of the largest cities in Australia (Brisbane, Canberra, Melbourne, Perth, Sydney) and two New Zealand cities (Auckland, Christchurch) for the period 1998-2001 (Barnett et al., 2006, 089770). The combined estimates showed that an increase of 0.75 ppm in the average 8-h max CO concentration over the current and previous day (lag 0-1) was associated with a 1.8% (95% CI: 0.7-2.8) increase in all CVD admissions among those aged 65+ yr. Among those aged 15-64 yr there was a smaller increase in CVD admissions (1.0% [95% CI: 0.2-1.7]). The second of the Australian studies examined ED visits for CVDs in older adults (65+ yr) in Sydney for the period 1997-2001 (Jalaludin et al., 2006, 189416). A 0.75 ppm increase in 8-h max CO concentration for single-day lags 0 and 1 was associated with increases in admissions of 2.5% (95% CI: 1.6-3.5) and 1.4% (95% CI: 0.5-2.4), respectively. Based on an average over lags 0 and 1 (e.g., lag 0-1), there was an increase of 2.6% (95% CI: 1.5-3.6). There were positive increases of approximately 3% in CVD ED visits during the cool (May-October) period but not the warm period (November-April).

Very few studies investigating the association between CO and cardiovascular hospital admissions have been conducted in European cities. Ballester et al. (2001, 013257) analyzed emergency hospital admissions in Valencia, Spain, for the period 1994-1996. The mean daily number of CVD admissions was 7, and there was no association between CO and admissions for all CVDs (RR: 1.009 [95% CI: 0.99-1.016] per 1 ppm increase in 1-h max CO concentration), heart diseases (RR: 1.010 [95% CI: 0.993-1.028] per 1 ppm increase), and cerebrovascular diseases (RR: 0.985 [95% CI: 0.959-1.012] per 1 ppm increase). When the analyses were stratified by hot and cold seasons, only CO concentrations during the hot season were associated with an increase in all cardiovascular admissions (RR: 1.033 [95% CI: 1.006-1.064] per 1 ppm increase), heart disease admissions (RR: 1.033 [95% CI: 1.000-1.067] per 1 ppm increase), and cerebrovascular admissions (RR: 1.074 [95% CI: 1.007-1.113] per 1 ppm increase).

Ballester et al. (2006, 088746) extended this research to include data from 14 Spanish cities for the period 1995-1999. An average exposure period over lags 0-1 was analyzed and for the combined estimates a 0.75 ppm increase in 8-h max CO concentration was associated with a 1.77% (95% CI: 0.56-2.99) increase in all cardiovascular hospital admissions and a larger increase of 3.57% (95% CI: 1.12-6.08) for heart disease admissions. These results persisted in two-pollutant models that included NO_2, O_3 and SO_2.

A study was carried out to evaluate the association between air pollution cardiovascular ED visits in subjects with and without diabetes in Sao Paulo, Brazil (Pereira Filho et al., 2008, 190260). From January 2001 to July 2003, 45,000 ED visits were registered due to CVDs, of which 700 were registered due to CVDs in diabetic patients. SO_2 and NO_2 were positively and statistically significantly associated with CVD ED visits among diabetics and nondiabetics, while CO was only positive and statistically significant among non-diabetic patients. PM_{10} and O_3 were not positively associated with ED admissions among either group.

Table 5-11 summarizes the non-specific CVD hospital admission studies that examined CO exposures. Due to the heterogeneity of endpoints, these studies do not lend themselves to a quantitative meta-analysis, and a forest plot was used to summarize the results of the studies on all CVD outcomes. Figure 5-5 shows the effect estimates associated with daily admissions for nonspecific CVD hospital admissions from selected studies.

In summary, many of the studies that examined associations between ambient CO concentrations and ED visits and daily hospital admissions for CVD reported small yet precise positive associations at short (0-1 day) lags. Among studies that conducted stratified analyses, there were slightly stronger effects among older adults and possibly during warmer periods.

Study	Location	Lag	Group
Bell et al. (2009, 193780)	126 US counties	0	65+ yr
Tolbert et al. (2007, 090316)	Atlanta, GA	0-2	
Linn et al. (2000, 002839)	Los Angeles, CA	0	All Year
Linn et al. (2000, 002839)	Los Angeles, CA	0	Spring
Linn et al. (2000, 002839)	Los Angeles, CA	0	Summer
Linn et al. (2000, 002839)	Los Angeles, CA	0	Fall
Linn et al. (2000, 002839)	Los Angeles, CA	0	Winter
Fung et al. (2005, 074322)	Windsor, Can	0-2	<65 yr
Fung et al. (2005, 074322)	Windsor, Can	0-2	65+ yr
Barnett et al. (2006, 089770)	Australia, New Zealand	0-1	15-64 yr
Barnett et al. (2006, 089770)	Australia, New Zealand	0-1	65+ yr
Jalaludin et al. (2006, 189416)	Sydney, Australia	0-1	65+ yr
Ballester et al. (2006, 088746)	Multicity, Spain	0-1	
Pereira Filho et al. (2008, 190260)	Sao Paulo, Brazil	0	Diabetic
Pereira Filho et al. (2008, 190260)	Sao Paulo, Brazil	0	Nondiabetic
Chang et al. (2005, 080086)	Taipei, Taiwan	0-2	>20°C Temp
Chang et al. (2005, 080086)	Taipei, Taiwan	0-2	<20°C Temp
Yang et al. (2004, 094376)	Kaohsiung, Taiwan	0-2	<20°C Temp
Yang et al. (2004, 094376)	Kaohsiung, Taiwan	0-2	>20°C Temp

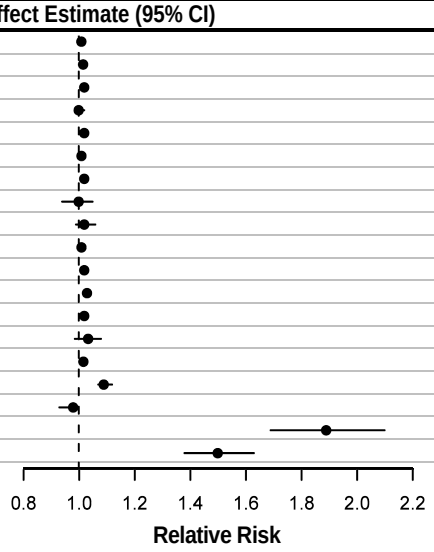


Figure 5-5. Summary of effect estimates (95% confidence intervals) associated with hospital admissions for CVD. Effect estimates have been standardized to a 1 ppm increase in ambient CO for 1-h max CO concentrations, 0.75 ppm for 8-h max CO concentrations, and 0.5 ppm for 24-h avg CO concentrations.

Table 5-11. Summary of nonspecific CVD hospital admission studies.

Study	Location	CVD Codes	Copollutants	Lags Examined	Upper CO Concentrations from AQS[b] in ppm	CO Concentrations Reported by Study Authors in ppm
Bell et al. (2009, 193780)	126 urban US counties (1999-2005)	Total CVD	$PM_{2.5}$, NO_2, EC	0, 1, 2	98th%: 1.1-19.1 99th%: 1.2-22.1 (1 h)	Median: 1.3 (1 h) Median: 0.5 (24 h)
Metzger et al. (2004, 044222)	Atlanta, GA (1993-2000)	All CVD	PM_{10}, NO_2, SO_2, O_3	0-2ma	98th%: 5.0-5.1 99th%: 5.5-5.9 (1 h)	Mean: 1.8 (1 h)
Peel et al. (2007, 090442)	Atlanta, GA (1993-2000)	All CVD	PM_{10}, NO_2, SO_2, O_3	0-2ma	98th%: 5.0-5.1 99th%: 5.5-5.9 (1 h)	Mean 1.8 (1 h)
Tolbert et al. (2007, 090316)	Atlanta, GA (1993-2004)	All CVD	PM_{10}, NO_2, SO_2, O_3	0-2ma	98th%: 4.7-4.9 99th%: 5.3-5.4 (1 h)	Mean 1.6 (1 h)
Linn et al. (2000, 002839)	Los Angeles, CA (1992-1995)	All CVD	PM_{10}, NO_2, O_3	0	98th%: 1.0-7.8 99th%: 1.1-8.3 (24 h)	Mean: (24 h) Winter 1.7; Spring 1.0; Summer 1.2; Fall 2.1
Slaughter et al. (2005, 073854)	Spokane, WA (1995-2001)	All CVD (ICD9: 390-459)	PM_{10}, $PM_{2.5}$, CO	1,2,3	98th%: 1.5-4.6 99th%: 1.7-5.0 (24 h)	Mean: range across 5 monitors 0.42-1.82 (24 h)
Fung et al. (2005, 074322)	Windsor, Can (1995-2000)	All CVD (HF, IHF, or Dysrhythmia)	PM_{10}, NO_2, SO_2, O_3	0, 0-1, 0-2	NA	Mean: 1.3 (1 h)
Chang et al. (2005, 080086)	Taipei, Taiwan (1997-2001)	All CVD (ICD9: 410-429)	PM_{10}, NO_2, SO_2, O_3	0-2	NA	Mean: 1.37 (24 h)
Yang et al. (2004, 094376)	Kaohsiung, Taiwan (1997-2000)	All CVD (ICD9: 410-429)	PM_{10}, NO_2, SO_2, O_3	0-2	NA	Mean: 0.79 (24 h)
Barnett et al. (2006, 089770)	Australia and New Zealand (1998-2001)	All CVD (ICD9: 390-459)	PM_{10}, NO_2, O_3	0-1	NA	Mean: (8h) 0.5-2.1
Jalaludin et al. (2006, 189416)	Sydney, Australia (1997-2001)	All CVD (ICD9: 390-459)	PM_{10}, NO_2, SO_2, O_3	0,1,2,3, 0-1	NA	Mean: 0.82 (8h)
Ballester et al. (2001, 013257)[a]	Valencia, Spain (1994-1996)	All CVD (ICD9: 390-459)	BS, NO_2, SO_2, O_3	1,2,3,4,5	NA	Mean: 0.54 (24 h)
Ballester et al. (2006, 088746)[a]	Multicity, Spain (1995-1999)	All CVD (ICD9: 390-459)	BS, PM_{10}, TSP, NO_2, SO_2, O_3	0-1	NA	Mean: range across 14 cities 0.12-0.24 (8h)
Pereira Filho et al. (2008, 190260)	Sao Paulo, Brazil (2001-2003)	All CVD	PM_{10}, NO_2, SO_2, O_3	0, 1, 2, 0-1, 0-2, 0-3	NA	Mean: 2.7 (8 h)

[a]These studies presented CO concentrations in the units mg/m^3. The concentrations were converted to ppm using the conversion factor 1 ppm = 1.15 mg/m^3, which assumes standard atmosphere and temperature.
[b] Includes range across individual monitors in study site; AQS data available for U.S. studies only.

Figure 5-6 and Figure 5-7 summarize the effects of CO concentration on ED visits and hospital admissions for all CVD outcomes other than stroke from studies that presented the results from two-pollutant models. Generally, the CO effect estimates from these studies are robust to the inclusion of copollutants, including PM_{10}, $PM_{2.5}$, NO_2, SO_2, and O_3. In all but two instances – Lee et al. (2007, 090707) (<25°C adjusted for NO_2) and Yang (2008, 157160) (<20°C adjusted for O_3) – when the single pollutant effect estimate was positive for CO, it remained positive after the addition of any of the copollutants investigated.

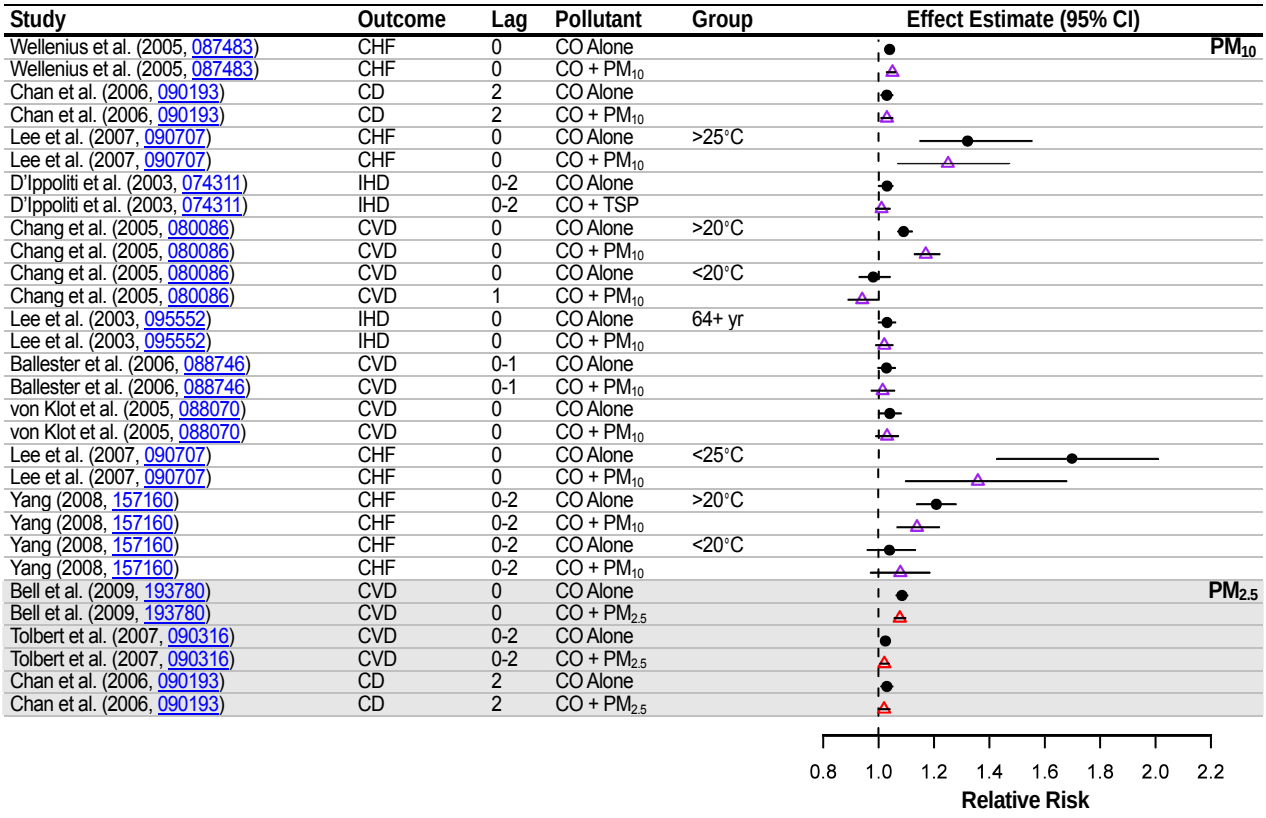


Figure 5-6. Effect estimates from studies of ED visits and hospital admissions for CVD outcomes other than stroke from single pollutant (CO only: black circles) and particulate copollutant (CO + $PM_{2.5}$: red triangles; CO + PM_{10} or TSP: purple triangles) models. Effect estimates have been standardized to a 1 ppm increase in ambient CO for 1-h max CO concentrations, 0.75 ppm for 8-h max CO concentrations, and 0.5 ppm for 24-h avg CO concentrations.

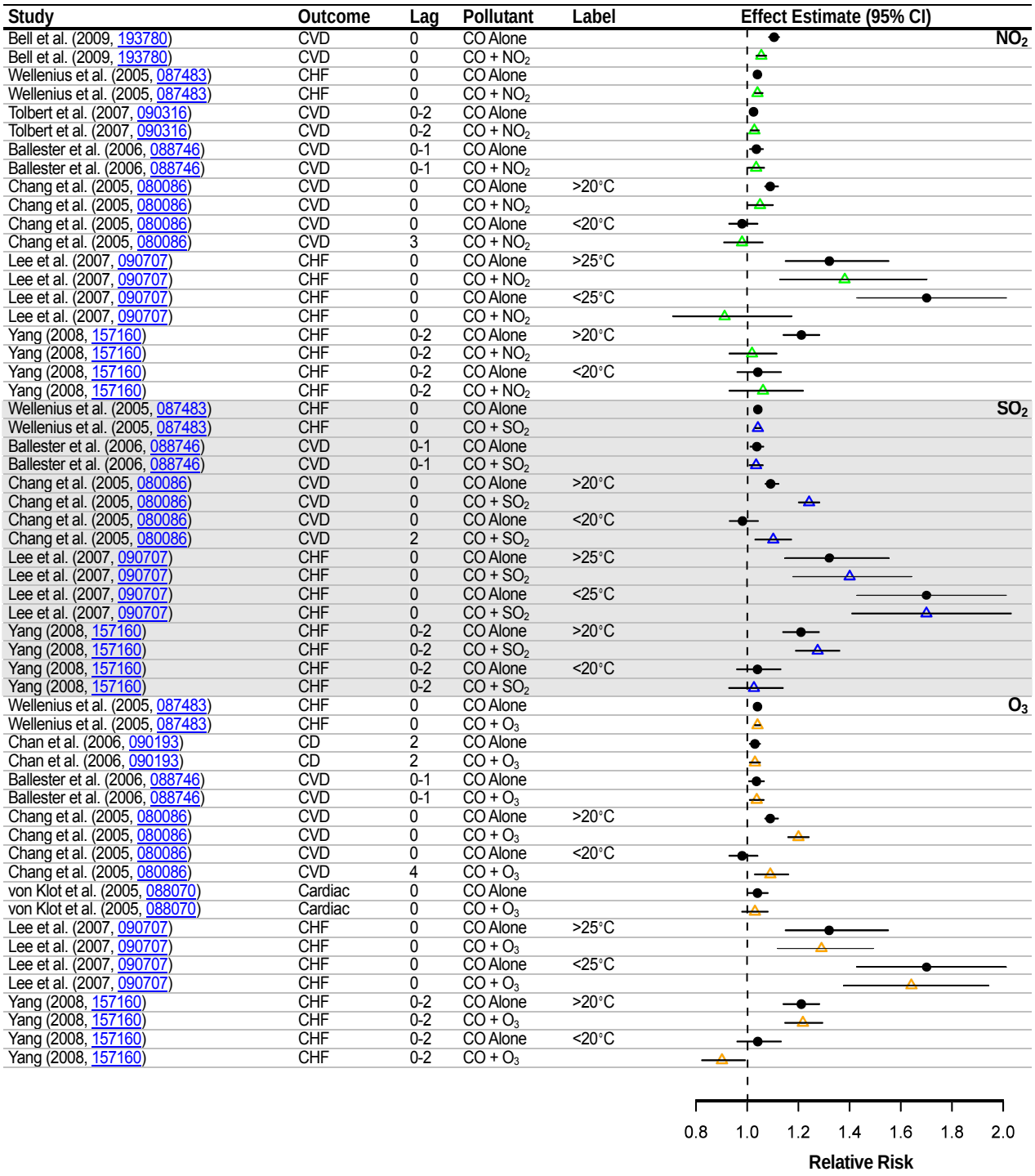


Figure 5-7. **Effect estimates from studies of ED visits and HAs for CVD outcomes other than stroke from single pollutant (CO only: black circles) and gaseous copollutant models (CO + NO_2, SO_2 and O_3= green, blue, and orange triangles, respectively). Effect estimates have been standardized to a 1 ppm increase in ambient CO for 1-h max CO concentrations, 0.75 ppm for 8-h max CO concentrations, and 0.5 ppm for 24-h avg CO concentrations.**

5.2.2. Epidemiologic Studies with Long-Term Exposure

Two studies examined CVD outcomes in association with long-term exposure to CO. Rosenlund et al. (2006, 089796) investigated long-term exposure (30 yr) to urban air pollution and the risk of MI in Sweden. The study included 2,246 cases and 3,206 controls aged 45-70 yr and residing in Stockholm County during 1992-1993. A detailed postal questionnaire was completed by 4,067 subjects, and all addresses inhabited during more than 2 yr since 1960 were geocoded. The exposures were then derived from dispersion calculations based on emissions data for each decade since 1960. These calculations were estimates of annual mean levels of traffic-generated NO_X, NO_2, CO, PM_{10}, and $PM_{2.5}$, with the addition of SO_2 from heating sources. The analyses were stratified by all cases, nonfatal cases, fatal cases, in-hospital death, and out-of-hospital death. Based on a 30-yr avg exposure all pollutants were not associated with overall MI incidence. However, increased CO was associated with out-of-hospital death from MI (OR: 1.81 [95% CI: 1.02-3.23] per 0.5 ppm increase in 30-yr avg CO concentration). Similar results were reported for NO_2. The correlation between the 30-yr NO_2 and CO exposures was reasonably strong (r = 0.74) and multipollutant models with both these pollutants included (NO_2, CO) were not examined. No other pollutants were significantly associated with all other MI outcomes. The study period was extended to include 43,275 cases of MI during 1985-1996 and 507,000 controls (Rosenlund et al., 2009, 190309). Five-year average exposures to NO_2, PM_{10} and CO were associated with incidence of MI, especially with fatal disease; when examining only nonfatal disease, no association was observed. The effect estimate for CO (OR: 1.03 [95%C CI: 1.02-1.04] per 0.5 ppm increase in 5-yr avg) was similar in magnitude to those for NO_2 and PM_{10}. When the analysis was restricted to the group that did not move between population censuses (the least expected misclassification of true individual exposure), the effect estimate for CO increased to 1.17 (95% CI: 1.11-1.24) per 0.5 ppm increase in 5-yr avg, and although the effect estimates for NO_2 and PM_{10} remained similar to the estimate for CO, in this analysis the effect estimate for CO was slightly greater in magnitude than the effect estimate for PM_{10}.

A small-area ecologic study analyzed mortality and hospital admissions for stroke across 1,030 census districts in Sheffield, U.K. (Maheswaran et al., 2005, 088683). Stroke counts within each census district were linked to modeled air pollution data which was then grouped into quintiles of exposure. For stroke hospital admissions, when the analyses were adjusted for only sex and age demographics, there was an exposure-response pattern exhibited across the quintiles of CO exposure with all levels reaching significance (RR: 1.37 [95% CI: 1.24-1.52] for the highest exposure group compared to the lowest group). However, this result did not persist when also adjusting for a deprivation index and smoking rates across the districts (RR: 1.11 [95% CI: 0.99-1.25]).

5.2.3. Summary of Epidemiologic Studies of Exposure to CO and Cardiovascular Effects

A substantial number of epidemiologic studies have examined the potential association between exposure to CO and various relevant cardiac endpoints or biomarkers. Overall, despite some mixed results reported among panel and retrospective cohort studies, there was evidence that exposure to CO has an effect on HR, various HRV parameters, and blood markers of coagulation and inflammation. Conversely, based on results from panel studies, there was little evidence of a link between CO and cardiac arrhythmia, cardiac arrest, the occurrence of MI, and increased BP.

Studies of ED visits and hospital admissions provide evidence that CO is associated with various forms of CVD, with lag periods ranging from 0 to 3 days. Nearly all of the studies include same day (lag 0) or next day (lag1) lag periods, which are consistent with the proposed mechanism and biological plausibility of these CVD outcomes. When categorized by specific cardiovascular outcome, the evidence is consistent. Studies of hospital admissions and ED visits for IHD provide the strongest evidence of ambient CO being associated with adverse CVD outcomes. The effect estimates for this outcome are nearly all positive, many are statistically significant, and the magnitude of effect is similar among the studies. Though not as consistent as the IHD effects, the effects for all CVD hospital admissions (which include IHD admissions) and CHF hospital admissions also provide evidence for an association with ambient CO concentrations. There is very limited evidence that ambient CO is associated with ischemic stroke. It is difficult to determine from this group of studies the extent to which CO is independently associated with CVD outcomes or if

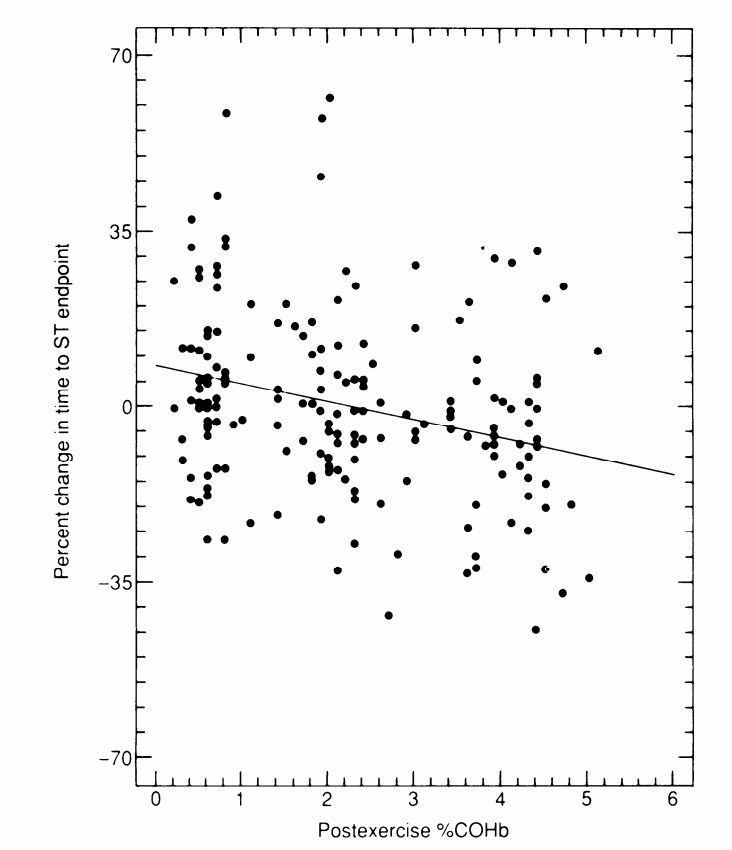
CO is a marker for the effects of another traffic-related pollutant or mix of pollutants. On-road vehicle exhaust emissions are a nearly ubiquitous source of combustion pollutant mixtures that include CO and can be an important contributor to CO in near-road locations. Although this complicates the efforts to disentangle specific CO-related health effects, the evidence indicates that CO associations generally remain robust in copollutant models and supports a direct effect of short-term ambient CO exposure on CVD morbidity.

5.2.4. Controlled Human Exposure Studies

Controlled human exposure studies provide valuable information related to the health effects of short-term exposure to air pollutants. Results of controlled human exposure studies can be used to provide coherence with the evidence from epidemiologic studies by expanding the understanding of potential mechanisms for the observed health outcomes. However, they may also provide information that can be used directly in quantitatively characterizing the exposure concentration-health response relationships at ambient or near-ambient concentrations.

Several human clinical studies cited in the 2000 CO AQCD (U.S. EPA, 2000, 000907) observed changes in measures of cardiovascular function among individuals with CAD, following short-term exposures to CO. Principal among these is a large multilaboratory study of men with stable angina (n = 63), designed to evaluate the effect of CO exposure resulting in COHb concentrations of 2% and 4% on exercise-induced angina and ST-segment changes indicative of myocardial ischemia (Allred et al., 1989, 013018; Allred et al., 1989, 012697; Allred et al., 1991, 011871). The majority of subjects were following an anti-ischemic medication regimen (e.g., beta blockers, nitrates, or calcium channel antagonists) which was maintained throughout the study. On three separate occasions, subjects underwent an initial graded exercise treadmill test, followed by 50- to 70-min exposures under resting conditions to average CO concentrations of 0.7 ppm (room air concentration range 0-2 ppm), 117 ppm (range 42-202 ppm) and 253 ppm (range 143-357 ppm). After the 50- to 70-min exposures, subjects underwent a second graded exercise treadmill test, and the percent change in time to onset of angina and time to ST endpoint between the first and second exercise tests was determined. The investigators conducted two exercise tests on exposure days (pre- versus postexposure) to control for day-to-day variability in the endpoints of interest. The effect of CO was evaluated by comparing the percent change in time to onset of angina or ST-segment change between the CO and clean air exposure days. The order of the three exposures was randomly determined and counterbalanced across subjects. For the CO exposure sessions, postexposure target COHb concentrations were set at values 10% greater than the post-exercise targets (i.e., 2.2% and 4.4%) to compensate for the elimination of CO during exercise testing in clean air following exposure. CO uptake constants were determined for each subject individually during a qualifying visit and were used to compute the inhaled concentration required to attain the target COHb concentrations. Although CO-oximetry was used at each center to rapidly provide approximate concentrations of COHb during the actual exposure, COHb concentrations determined by a gas chromatographic technique were used in the statistical analyses as this method is known to be more accurate than CO-oximetry and other spectrophotometric methods, particularly for samples containing COHb concentrations <5%. For the two CO exposures, the average postexposure COHb concentrations were reported as 2.4% and 4.7% (3.2% and 5.6% using CO-oximetry), and the average post-exercise COHb concentrations were reported as 2.0% and 3.9% (2.7% and 4.7% using CO-oximetry). While the average COHb concentrations during the exercise tests were clearly between the concentrations measured in postexposure and post-exercise blood samples, the study authors noted that the samples at the end of the exercise test represented the COHb concentrations at the approximate time of onset of myocardial ischemia as indicated by angina and ST segment changes. Relative to clean air exposure (COHb ≈ 0.6-0.7%), exposures to CO resulting in post-exercise COHb concentrations of 2.0% and 3.9% were shown to decrease the time required to induce ST-segment changes by 5.1% ($p = 0.01$) and 12.1% ($p < 0.001$), respectively. These changes were well correlated with the onset of exercise-induced angina. The observed dose-response relationship was further evaluated by regressing the percent change in time to ST-segment change or time to angina on actual post-exercise COHb concentration (0.2-5.1%) using the three exposures (air control and two CO exposures) for each subject. Regression analyses were conducted separately for each individual and the averages of the intercepts and slopes across subjects were reported. This analysis demonstrated significant decreases in time to angina and ST-segment change of approximately 1.9% and 3.9%, respectively, per 1% increase in COHb concentration, with no evidence of a measurable

threshold. The relationship between percent change in time to ST-segment endpoint and post-exercise COHb concentration is illustrated in Figure 5-8.



Source: Reprinted with Permission of HEI from Allred et al. (1989, 012697)

Figure 5-8. Regression of the percent change in time to ST endpoint between the pre- and postexposure exercise tests ([postexposure–pre-exposure]/pre-exposure) and the measured blood COHb levels at the end of exercise for the 63 subjects combined. The line represents the average of individual regressions.

In addition to the work of Allred et al. (1989, 013018; 1989, 012697; 1991, 011871) a number of other studies involving individuals with stable angina have also demonstrated a CO-induced decrease in time to onset of angina, as well as reduction in duration of exercise at COHb concentrations between 3 and 6%, measured using spectrophotometric methods (Adams et al., 1988, 012692; Anderson et al., 1973, 023134; Kleinman et al., 1989, 012696; Kleinman et al., 1998, 047186). However, Sheps et al. (1987, 012212) observed no change in time to onset of angina or maximal exercise time following a 1-h exposure to 100 ppm CO (targeted COHb of 4%) among a group of 30 patients with CAD. In a subsequent study conducted by the same laboratory, a significant increase in number of ventricular arrhythmias during exercise was observed relative to room air among individuals with CAD following a 1-h exposure to 200 ppm CO (targeted COHb of 6%) but not following a 1-h exposure to 100 ppm CO (targeted COHb of 4%) (Sheps et al., 1990, 013286).

While cardiovascular effects of CO have consistently been observed in studies of controlled human exposure among individuals with CAD at COHb concentrations between 2 and 6%, a quantitative meta-analysis of these studies is of limited value considering differences in the methods used. For example, variation in exercise protocols resulted in substantial differences between studies in total exercise time. More importantly, only Allred et al. (1989, 013018; 1989, 012697; 1991,

011871) analyzed COHb concentration using gas chromatography. Although all studies measured COHb using spectrophotometric methods, these methods are only accurate within approximately 1% COHb of the true value at COHb concentrations < 5% (U.S. EPA, 1991, 017643). Therefore, a quantitative evaluation of changes in cardiovascular response with small increases in COHb concentration (< 1%) as measured using CO-oximetry is neither appropriate nor informative, particularly at low COHb concentrations.

It should be noted that although the subjects evaluated in the studies described above are not necessarily representative of the most sensitive population, the level of disease in these individuals was moderate to severe, with the majority either having a history of MI or having ≥ 70% occlusion of one or more of the coronary arteries. The 2000 CO AQCD (U.S. EPA, 2000, 000907) presented very little evidence of CO-induced changes in cardiovascular function in healthy adults. Davies and Smith (1980, 011288) exposed healthy young adults continuously for 7 days to CO concentrations of 0, 15, or 50 ppm. In this study, a marked ST-segment depression was demonstrated in only 1 out of 16 subjects following exposure to 15 ppm CO (2.4% COHb) or 50 ppm CO (7.2% COHb).

Since the publication of the 2000 CO AQCD (U.S. EPA, 2000, 000907), no new human clinical studies have been published involving controlled CO exposures among subjects with CAD. However, a number of new studies have evaluated changes in various measures of cardiovascular and systemic responses following controlled exposures to CO in healthy adults. Adir et al. (1999, 001026) exposed 15 young healthy adult males to room air or CO for approximately 4 min, using a CO exposure concentration which had been shown to produce the targeted COHb level of 4-6%. Following each exposure, subjects performed an exercise treadmill test at their maximal capacity. Exposure to CO was not observed to cause arrhythmias, ST-segment changes, or changes in myocardial perfusion (thallium scintigraphy) during postexposure exercise. However, CO was demonstrated to decrease the postexposure duration of exercise by approximately 10% ($p = 0.0012$). In addition, the authors reported significant CO-induced decreases in metabolic equivalent units ($p < 0.001$), which is a relative measure of O_2 consumption. These results support the findings of several studies cited in the 2000 CO AQCD (U.S. EPA, 2000, 000907) which observed decreases in exercise duration and maximal aerobic capacity among healthy adults at COHb levels ≥ 3% (Drinkwater et al., 1974, 041332; Ekblom and Huot, 1972, 010886; Horvath et al., 1975, 010887; Raven et al., 1974, 041340). While these decreases in exercise duration were relatively small and only likely to be noticed by competing athletes, the findings are nonetheless important in providing coherence with the observed effects of CO on exercise-induced myocardial ischemia among patients with CAD.

Kizakevich et al.(2000, 052691) evaluated the cardiovascular effects of increasing CO concentration in healthy adults engaged in upper and lower body exercise. Subjects were initially exposed for 4-6 min to CO concentrations between 1,000 and 3,000 ppm, followed by continued exposure to 27, 55, 83, and 100 ppm to maintain COHb levels of 5, 10, 15, and 20%, respectively. Relative to room air control, CO exposure was not observed to cause ST-segment changes or affect cardiac rhythm at any concentration during either upper or lower body exercise. Compensation mechanisms for reduced O_2 carrying capacity during CO exposure were demonstrated, with statistically significant increases in heart rate occurring at COHb levels ≥ 5%, and statistically significant increases in cardiac output and cardiac contractility observed at COHb levels ≥ 10%. In a human clinical study designed to evaluate the contribution of CO to cardiovascular morbidity associated with cigarette smoking, Zevin et al. (2001, 021120) exposed 12 healthy male smokers for 7 consecutive days to clean air, CO, or cigarette smoke, with each subject serving as his own control. The COHb levels were similar between the exposures to cigarette smoke and CO, with average concentrations of 6% and 5%, respectively. Cigarette smoke, but not CO, was observed to significantly increase plasma levels of CRP and plasma platelet factor 4 relative to the air control arm of the study. Neither cigarette smoke nor CO was shown to affect BP. Hanada et al. (2003, 193915) observed an increase in leg muscle sympathetic nerve activity (MSNA) following controlled exposures to CO (COHb ≈ 20%) under normoxic or hyperoxic conditions. Although an increase in the magnitude of sympathetic activation is typically associated with regional vasoconstriction, no CO-induced changes in femoral venous blood flow were observed in this study. These findings are in agreement with those of Hausberg and Somers (1997, 083450) who observed no change in forearm blood flow or BP in a study of 10 healthy men and women following a controlled exposure to CO (COHb ≈ 8%). Interestingly, one recent study did observe an increase in retinal blood flow, retinal vessel diameter, and choroidal blood flow following controlled exposures to CO at a concentration of 500 ppm (Resch et al., 2005, 193853). This protocol resulted in COHb concentrations of 5.6% and 9.4% following exposures of 30 and 60 min, respectively, with

statistically significant increases in retinal and choroidal blood flow observed at both time points relative to synthetic air control. This CO-induced change in ocular hemodynamics may have been due to local tissue hypoxia; however, the clinical significance of this finding is unclear. Exposures to CO have also been shown to affect skeletal muscle function, with one recent human clinical study reporting a decrease in muscle fatigue resistance in healthy adult males, using both voluntary and electrically-induced contraction protocols following controlled exposures to CO resulting in an average COHb level of 6% (Morse et al., 2008, 097980).

In summary, controlled human exposures to CO among individuals with CAD have been shown to consistently increase markers of myocardial ischemia at COHb concentrations between 2 and 6%. No such effects have been observed in healthy adults following controlled exposures to CO. Although some studies have reported CO-induced hemodynamic changes among healthy adults at COHb concentrations as low as 5%, this effect has not been observed consistently across studies.

5.2.5. Toxicological Studies

While there was no toxicological research reported in the 2000 CO AQCD (U.S. EPA, 2000, 000907) that involved CO exposures at or below the NAAQS levels, adverse cardiovascular effects were reported for higher CO concentrations. The lowest observed effect levels for cardiovascular effects in experimental animals included 50 ppm (6-wk exposure, 2.6% COHb) for cardiac rhythm effects, 100 ppm (46 days, 9.3% COHb) for hematology effects, 150 ppm (30 min, 7.5% COHb) for hemodynamic effects, 200 ppm (30 days, 15.8% COHb) for cardiomegaly, and 250 ppm (10 wk, 20% COHb) for atherosclerosis and thrombosis (Table 6-11 in the 2000 CO AQCD) (U.S. EPA, 2000, 000907). Conflicting experimental data relating to the role of CO in promoting atherosclerotic vessel disease were discussed. While some animal studies have linked chronic CO exposure with atherosclerosis development resulting from increased fatty streaking and cellular lipid loading (Davies et al., 1976, 010660; Thomsen, 1974, 010704; Turner et al., 1979, 012328), other studies have failed to see this association (Penn et al., 1992, 013728; Stupfel and Bouley, 1970, 010557). Vascular insults due to acute exposure to CO concentrations of 50 ppm and higher were also reported (Ischiropoulos et al., 1996, 079491; Thom, 1993, 013895; Thom et al., 1998, 016750; Thom et al., 1999, 016757; Thom et al., 1999, 016753). In addition, chronic CO exposure has been shown to result in ventricular hypertrophy (Penney et al., 1984, 011567; Penney et al., 1988, 012521).

The following sections describe recent studies dealing with toxicity of low to moderate concentrations (35-250 ppm) of CO. There has been little new research with the overt purpose of examining environmentally-relevant levels of CO. For the most part, studies were designed to mimic exposures related to cigarette smoke, either side-stream or mainstream, accidental CO poisoning, or for the purposes of therapeutic application. Thus, few studies examined levels of CO within the current 1-h (35 ppm) or 8-h (9 ppm) NAAQS levels, and fewer still examined concentration response curves to delineate no-effects levels. However, it is apparent that CO, at low to moderate concentrations, has pathophysiologic effects on the cardiovascular system and on relatively ubiquitous cellular pathways. In evaluating these studies, it should be kept in mind that the traditional concept of CO pathophysiology resulting from reduced O_2 delivery is likely to be more relevant for higher concentrations of CO than are currently found in the ambient environment.

CO exposure at environmentally-relevant levels is unlikely to cause overt toxicity in a healthy cell; however, susceptibility may be rendered by disease or developmental stage. A common theme appears to be the vulnerability of vascular cells, especially the endothelium, which could be considered the first organ of contact once CO is taken up into the circulation. While relatively little research has been conducted since the 2000 CO AQCD (U.S. EPA, 2000, 000907), several key studies conducted at environmentally-relevant CO levels provide important clues to the potential public health implications of ambient CO exposure.

5.2.5.1. Endothelial Dysfunction

While the preferential binding to heme and effective displacement of O_2 by CO has been well established for over a century, new information from various fields of study are beginning to elucidate nonhypoxic mechanisms that may lead to cardiovascular abnormalities associated with CO exposure. Research by Thom, Ischiropoulos, and colleagues (Ischiropoulos et al., 1996, 079491; Thom and Ischiropoulos, 1997, 085644; Thom et al., 1994, 076459; Thom et al., 1997, 084337;

Thom et al., 1999, 016753; Thom et al., 1999, 016757), some of which was reported in the 2000 CO AQCD (U.S. EPA, 2000, 000907), has focused on CO-mediated displacement of NO from heme-binding sites. Some of this work demonstrates a specific pathway by which severe CO poisoning can lead to the release of NO from platelets with subsequent neutrophil activation and vascular injury (Ischiropoulos et al., 1996, 079491; Thom et al., 2006, 098418). The steps include: (1) peroxynitrite generation from the reaction of NO from platelets with neutrophil-derived superoxide; followed by (2) stimulation of intravascular neutrophil degranulation; that can result in (3) myeloperoxidase deposition along the vascular lining. Products from myeloperoxidase-mediated reactions can cause endothelial cell activation (Thom et al., 2006, 098418) and can lead to endothelial dysfunction. The concentrations used in these studies are greatly in excess of the NAAQS levels but certainly within the range of accidental or occupational exposures. Research by these same investigators at more environmentally-relevant CO levels was partially reviewed in the 2000 CO AQCD (U.S. EPA, 2000, 000907). The release of free NO was noted in isolated rat platelets exposed to 10-20 ppm CO (Thom and Ischiropoulos, 1997, 085644). Increased nitrotyrosine content of the aorta was observed in rats exposed to 50 ppm CO for 1 h (Thom et al., 1999, 016757; Thom et al., 1999, 016753). Furthermore, in this same study, a 1-h exposure to 100 ppm CO led to albumin efflux from skeletal muscle microvasculature at 3 h and leukocyte sequestration in the aorta at 18 h; LDL oxidation was also reported. These effects were dependent on NOS but not on neutrophils or platelets. A second study demonstrated NO-dependent effects of 50-100 ppm CO in lungs and is described in Section 5.5.4 (Thom et al., 1999, 016757). Studies in cultured endothelial cells were also conducted using buffer saturated with 10-100 ppm CO (Thom et al., 1997, 084337). These experiments were designed to mimic conditions where blood COHb levels were between 3.8 and 28%, resulting in exposure of endothelial cells to 11-110 nM CO. CO stimulated the release of NO from endothelial cells along with formation of peroxynitrite; delayed cell death was observed at CO concentrations of 22 nM and higher (Thom et al., 1997, 084337). A more recent study demonstrated adaptive responses in endothelial cells exposed to this same range of CO concentrations (Thom et al., 2000, 011574). Specifically, 1-h exposure to 11 nM CO resulted in MnSOD and HO-1 induction and resistance to the apoptotic effects of 110 nM CO. These protective effects of CO were mediated by NO, as demonstrated using an inhibitor of NOS and a scavenger of peroxynitrite. Collectively, these experiments demonstrated oxidative and nitrosative stress, the initiation of inflammation, increased microvascular permeability and altered cell signaling in animals and isolated cells following exposure to 10-100 ppm CO.

CO is an endogenous regulator of vasomotor tone through vasodilatory effects, mediated by activation of soluble guanylate cyclase and activation of large conductance Ca^{2+}-activated K^{+} channels. However, CO does not cause vasodilation in every vascular bed. For example, 5, 100, 500 and 2,500 ppm CO administered by inhalation to near-term fetal lambs did not induce pulmonary vasodilation, and the HO-inhibitor zinc protoporphyrin IX failed to affect baseline vascular tone (Grover et al., 2000, 097088). In some cases CO promotes vasoconstriction, which is thought to be mediated by inhibition of endothelial NOS (Johnson and Johnson, 2003, 053611; Thorup et al., 1999, 193782) or decreased NO bioavailability. An interesting series of studies has also suggested that endogenous CO derived from HO-1 which is induced in a variety of disease models (salt-sensitive forms of hypertension, metabolic syndrome in obese rats) is responsible for skeletal muscle arterial endothelial dysfunction (Johnson and Johnson, 2003, 053611; Johnson et al., 2006, 193874; Teran et al., 2005, 193770). Additional studies will be useful in determining whether environmentally-relevant concentrations of CO have detrimental effects on preexisting conditions such as hypertension, metabolic syndrome or pregnancy.

Several recent animal studies examined the vascular effects of controlled exposures to complex combustion mixtures containing CO. Vascular dilatation was decreased following exposure to diesel (4 h at 4 ppm) (Knuckles et al., 2008, 191987) and gasoline engine emissions (6 h/day for 1, 3, and 7 days at 80 ppm) (Lund et al., 2009, 180257). Furthermore, evidence of vascular ROS following gasoline emissions has been shown in certain animal models (6 h/day for 50 days at 8-80 ppm) (Lund et al., 2007, 125741). While none of these studies examined the potential independent role of CO, it is clearly a common factor in the various combustion atmospheres, and future work will be needed to reveal its importance on vascular health.

5.2.5.2. Cardiac Remodeling Effects

Cardiomyopathy, or abnormal growth of the cardiac muscle, can manifest in different ways, depending on the nature of the insult. The adverse effects of cardiac hypertrophy are due to reduction of ventricular chamber volume and a diminishing efficiency of the heart. Such concentric hypertrophy typically occurs in response to chronic increases in load, as occurs with hypertension. Ischemia of the cardiac tissue can also lead to cardiac remodeling and myopathy. During and after an acute infarction or obstruction of major coronary vessels, downstream tissues can suffer severe regional ischemia that leads to significant necrosis. Such regions will lose the ability to contract, and surrounding tissue will show deficits in contractility. Decreased contractility is often a result of structural thinning of the ventricular wall, as well as metabolic impairments. Chronic ischemia, such as may result from CAD, may similarly impair cardiomyocyte function and cause decreased contractility and remodeling. However, ultimately cardiomyopathies are of a complex origin involving mismanagement of fluid balance, abnormal hormonal influences (epinephrine, angiotensin), and insufficient perfusion/nutrition. Assessing the role of exogenous CO in altering pathways leading to cardiomyopathy is a relatively new endeavor, and several new findings are of great interest.

The heart is a known target for CO toxicity, potentially due to its high rate of O_2 consumption. Effects of CO on the healthy heart have only been observed at relatively high concentrations. For example, a recent study by Sorhaug et al. (2006, 180414) demonstrated cardiac hypertrophy in rats exposed for 72 wk to 200 ppm CO. COHb levels were reported to be 14.7%. Neither structural signs of hypertension in the pulmonary arteries nor atherosclerotic lesions in the systemic arteries were observed. A follow-up study by the same investigators (Bye et al., 2008, 193777) found reduced aerobic capacity and contractile function leading to pathologic cardiac hypertrophy in rats exposed for 18 mo to 200 ppm CO. Cardiac hypertrophy was also demonstrated in rats exposed to 100-200 ppm CO for 1-2 wk (Loennechen et al., 1999, 011549). This response was accompanied by an increase in endothelin-1 expression. COHb levels were reported to be 12-23% in this latter study.

Effects of CO on the healthy heart have also been demonstrated following short-term exposures. In a study by Favory et al. (2006, 184462) rats were exposed to 90 min of 250 ppm CO, which led to peak COHb values of roughly 11%; recovery of 96 h was needed for COHb levels to return to baseline. The authors noted that within the first 24 h of recovery, while COHb values decreased from 11% to 5%, the coronary vascular perfusion pressure and the left ventricular developed pressure were significantly increased compared to baseline. Concomitantly, the ratio of cGMP to cAMP decreased, and the sensitivity of the coronary vascular bed to both acetylcholine and a NO donor was reduced by CO exposure. The authors concluded that the discordant alterations in contractility (increased) and perfusion (decreased) may place the heart at risk of O_2 limitations following this exposure to CO.

Several studies examined the impact of lower levels (50 ppm) on preexisting or concurrent cardiac pathologies. In one such study, CO exacerbated the effects of a hypoxia-based model of right ventricular remodeling and failure (Gautier et al., 2007, 096471). In controlled laboratory settings, chronic hypobaric hypoxia (HH) caused right ventricular hypertrophy as a result of pulmonary arterial vasoconstriction and increased pulmonary resistance. Using such a model (Wistar rats exposed for 3 wk to hypoxia), CO (50 ppm during the last week of hypoxia, continuous) only increased COHb from 0.5% to 2.4% in the hypoxia model, yet had significant effects on blocking compensatory functional responses to hypoxia, such as increased fractional shortening and contractility. Also, while right ventricular weight was increased by hypoxia alone, significant pathology related to necrosis was observed in the hypoxia + CO-exposed rats. The reduced coronary perfusion of the right ventricle in hypoxia + CO-exposed rats may help explain the histopathologic findings. The authors cited previous work demonstrating that exogenous CO can inhibit NOS (Thorup et al., 1999, 193782), which is essential for coronary dilation and angiogenesis. Thus, this study provided evidence that exogenous CO may interrupt or downregulate pathways that endogenous CO may activate.

In two studies by Melin et al. (2002, 037502; 2005, 193833), Dark Agouti rats were exposed for 10 wk to either HH, 50 ppm CO or HH plus 50 ppm CO. CO exposure amplified the right ventricular cardiac hypertrophy and decreased the right ventricular diastolic function which occurred in response to HH. In addition, the combined exposure led to effects on left ventricular morphology and function which were not seen with either exposure alone. Changes in HRV were also reported. Results from both of these studies combined with results of Gautier and colleagues (Gautier et al., 2007, 096471) indicated that CO may interfere with normal homeostatic responses to hypoxia. This

could occur by blocking HIF-1α-responsive elements (vascular endothelial growth factor, erythropoietin) or other cell signaling pathways.

In a similar study, Carraway et al. (2002, 026018) exposed rats to HH (380 torr) with or without co-exposure to CO (50 ppm). These exposures were continuous for up to 21 days and focused on pulmonary vascular remodeling. While the addition of CO to HH did not alter the thickness or diameter of vessels in the lung, there was a significant increase in the number of small (<50 μm) diameter vessels compared to control, HH-only, and CO-only exposures. Despite the greater number of vessels, the overall pulmonary vascular resistance was increased in the combined CO + hypoxic exposure, which the authors attributed to enhancement of muscular arterioles and β-actin. Results of this study, taken together with results from the studies of Gautier et al. (2007, 096471) and Melin et al. (2002, 037502; 2005, 193833), suggested that the combined effect of low levels of CO with hypoxia is an enhanced right ventricle workload and an exacerbated cardiomyopathy related to pulmonary hypertension. The population at risk of primary pulmonary hypertension is low, but secondary pulmonary hypertension is a frequent complication of COPD and certain forms of heart failure.

5.2.5.3. Electrocardiographic Effects

In two related studies, Wellenius et al. (2004, 087874; 2006, 156152) examined the effects of CO in an animal model of post-infarction myocardial sensitivity (Wellenius et al., 2002, 025405). In a previous study, ECG changes were observed during exposure to residual oil fly ash (ROFA) particles in anesthetized post-MI Sprague Dawley rats (Wellenius et al., 2002, 025405). Using this model, Wellenius and colleagues tested the effects of 35 ppm CO (1-h exposure) on the induction of spontaneous arrhythmias (Wellenius et al., 2004, 087874). CO exposure caused a statistically significant decrease (60.4%) in ventricular premature beat (VPB) frequency during the exposure period in rats with a high number of pre-exposure VPB. No interaction was observed with co-exposure to carbon concentrated particles, which independently reduced VPB frequency during the postexposure period when administered alone. In a follow-up publication, results from the analysis of supraventricular ectopic beats (SVEB) were provided (Wellenius et al., 2006, 156152). A decrease in the number of SVEB was observed with CO (average concentration 37.9 ppm) compared to filtered air. While the authors concluded that CO exposure did not increase risk of SVEB in this particular rodent model of coronary occlusion, the fact that cardiac electrophysiological dynamics are significantly altered by short-term exposure to low-level CO may be of concern for other models of susceptibility.

5.2.5.4. Summary of Cardiovascular Toxicology

Experimental studies demonstrated that short-term exposure to 50-100 ppm CO resulted in aortic injury as measured by increased nitrotyrosine and the sequestration of activated leukocytes in healthy rats. In addition, skeletal muscle microvascular permeability was increased. Short-term exposure to 35 ppm CO altered cardiac electrophysiology in a rat model of arrhythmia. Furthermore, short-term exposure to 50 ppm CO exacerbated cardiac pathology and impaired function in an animal model of hypertrophic cardiomyopathy and enhanced vascular remodeling and increased pulmonary vascular resistance in an animal model of pulmonary hypertension. Ventricular hypertrophy was observed in healthy rats in response to chronic exposures of 100-200 ppm CO. These studies provide some support for the development of adverse health effects resulting from exposures to CO at environmentally-relevant concentrations.

5.2.6. Summary of Cardiovascular Effects

5.2.6.1. Short-Term Exposure to CO

The most compelling evidence of a CO-induced effect on the cardiovascular system at COHb levels relevant to the current NAAQS comes from a series of controlled human exposure studies among individuals with CAD. These studies, described in the 1991 (U.S. EPA, 1991, 017643) and

2000 (U.S. EPA, 2000, 000907) CO AQCDs, demonstrate consistent decreases in the time to onset of exercise-induced angina and ST-segment changes following CO exposures resulting in COHb levels of 2-6% (Section 5.2.4). No human clinical studies have been designed to evaluate the effect of controlled exposures to CO resulting in COHb concentrations lower than 2%. Human clinical studies published since the 2000 CO AQCD (U.S. EPA, 2000, 000907) have reported no association between CO and ST-segment changes or arrhythmia; however, none of these studies included individuals with diagnosed heart disease.

While the exact physiological significance of the observed ST-segment changes among individuals with CAD is unclear, ST-segment depression is a known indicator of myocardial ischemia. It is also important to note that the individuals with CAD who participated in these controlled exposure studies may not be representative of the most sensitive individuals in the population. It is conceivable that the most sensitive individuals respond to COHb concentrations lower than those evaluated in studies of controlled human exposures. Variability in activity patterns and severity of disease among individuals with CAD is likely to influence the critical level of COHb which leads to adverse cardiovascular effects.

The degree of ambient CO exposure which leads to attainment of critical levels of COHb will also vary between individuals. Although endogenous COHb is generally <1% in healthy individuals, higher endogenous COHb levels are observed in individuals with certain medical conditions. Nonambient exposures to CO, such as exposure to ETS, may increase COHb above endogenous levels, depending on the gradient of pCO. Ambient exposures may cause a further increase in COHb. Modeling results described in Chapter 4 indicate that increases of ~1% COHb are possible with exposures of several ppm CO, depending on exposure duration and exercise level.

Findings of epidemiologic studies conducted since the 2000 CO AQCD (U.S. EPA, 2000, 000907) are coherent with results of the controlled human exposure studies. These recent studies observed associations between ambient CO concentration and ED visits and hospital admissions for IHD, CHF and cardiovascular disease as a whole and were conducted in locations where the mean 24-h avg CO concentrations ranged from 0.5 ppm to 9.4 ppm (Table 5-7). All but one of these studies that evaluated CAD outcomes (IHD, MI, angina) reported positive associations (Figure 5-2). Although CO is often considered a marker for the effects of another traffic-related pollutant or mix of pollutants, evidence indicates that CO associations generally remain robust in copollutant models and supports a direct effect of short-term ambient CO exposure on CVD morbidity. These studies add to findings reported in the 2000 CO AQCD (U.S. EPA, 2000, 000907) that demonstrated associations between short-term variations in ambient CO concentrations and exacerbation of heart disease.

The known role of CO in limiting O_2 availability lends biological plausibility to ischemia-related health outcomes following CO exposure. However, it is not clear whether the small changes in COHb associated with ambient CO exposures results in substantially reduced O_2 delivery to tissues. Recent toxicological studies suggest that CO may also act through other mechanisms by initiating or disrupting cellular signaling. Studies in healthy animals demonstrated oxidative injury and inflammation in response to 50-100 ppm CO, while studies in animal models of disease demonstrated exacerbation of cardiomyopathy and increased vascular remodeling in response to 50 ppm CO. Further investigations will be useful in determining whether altered cell signaling contributes to adverse health effects following ambient CO exposure.

Given the consistent and coherent evidence from epidemiologic and human clinical studies, along with biological plausibility provided by CO's role in limiting O_2 availability, it is concluded that **a causal relationship is likely to exist between relevant short-term exposures to CO and cardiovascular morbidity.**

5.2.6.2. Long-Term Exposure to CO

Only two epidemiologic studies were identified that investigated the relationship between long-term exposure to CO and cardiovascular effects, and the results of these studies provide very limited evidence of an association. Considering the lack of evidence from controlled human exposure studies and the very limited evidence from toxicological studies on cardiovascular effects following long-term exposure to CO, the available evidence is **inadequate to conclude that a causal relationship exists between relevant long-term exposures to CO and cardiovascular morbidity.**

5.3. Central Nervous System Effects

5.3.1. Controlled Human Exposure Studies

The behavioral effects of controlled human exposures to CO have been examined by several laboratories, and these studies were summarized in the 2000 CO AQCD (U.S. EPA, 2000, 000907). Briefly, decreases in visual tracking as well as visual and auditory vigilance were observed following exposures to CO resulting in COHb levels between 5% and 20% (Benignus et al., 1987, 012250; Fodor and Winneke, 1972, 011041; Horvath et al., 1971, 011075; Putz et al., 1979, 023137). One study reported similar behavioral effects (time discrimination) among a group of healthy volunteers with COHb levels <3% (Beard and Wertheim, 1967, 011015), though subsequent studies were unable to replicate these findings at such low exposure concentrations (Otto et al., 1979, 010863; Stewart et al., 1973, 093412). These outcomes represent a potentially important adverse effect of CO exposure resulting in COHb levels ≥ 5%, although it is important to note that these findings have not been consistent across studies. Similarly, some studies demonstrated decreases in reaction time as well as decrements in cognitive function and fine motor skills following controlled exposures to CO; however, these studies were not typically conducted using double-blind procedures, which may significantly affect the outcome of behavioral studies (Benignus, 1993, 013645). It should be noted that all behavioral studies of controlled CO exposure were conducted in normal, healthy adults. No new human clinical studies have evaluated CNS or behavioral effects of exposure to CO.

5.3.2. Toxicological Studies

The evidence for toxicological effects of CO exposure in laboratory animal models comes from in utero or perinatal exposure involving relatively low to relatively high concentrations of CO (12.5-750 ppm). Affected endpoints from this early, developmental CO exposure include behavior, memory, learning, locomotor ability, peripheral nervous system myelination, auditory decrements, and neurotransmitter changes. These data are addressed in detail in the Birth Outcomes and Developmental Effects section of the ISA (Section 5.4.2). Further, a group of studies have found that exposure to high concentrations of CO (500-1,200 ppm) can result in CO-dependent ototoxicity, specifically loss of threshold of cochlear compound action potentials (CAP) and potentiation of noise-induced hearing loss (NIHL) (Chen et al., 2001, 193985; Fechter et al., 1997, 081322; Fechter et al., 2002, 193926; Liu and Fechter, 1995, 076524). Proposed mechanisms for these effects include ROS generation and glutamate release.

5.3.3. Summary of Central Nervous System Effects

Exposure to high levels of CO has long been known to adversely affect CNS function, with symptoms following acute CO poisoning including headache, dizziness, cognitive difficulties, disorientation, and coma. However, the relationship between ambient levels of CO and neurological function is less clear and has not been evaluated in epidemiologic studies. Studies of controlled human exposures to CO discussed in the 2000 CO AQCD (U.S. EPA, 2000, 000907) reported inconsistent neural and behavioral effects following exposures resulting in COHb levels of 5-20%. No new human clinical studies have evaluated central nervous system or behavioral effects of exposure to CO. At ambient-level exposures, healthy adults may be protected against CO-induced neurological impairment owing to compensatory responses including increased cardiac output and cerebral blood flow. However, these compensatory mechanisms are likely impaired among certain potentially susceptible groups, including individuals with reduced cardiovascular function.

Toxicological studies that were not discussed in the 2000 CO AQCD (U.S. EPA, 2000, 000907) employed rodent models to show that low to moderate CO exposure during the in utero or perinatal period can adversely affect adult outcomes, including behavior, neuronal myelination, neurotransmitter levels or function, and the auditory system (discussed in Section 5.4). In utero CO exposure, including both intermittent and continuous exposure, has been shown to impair multiple behavioral outcomes in offspring including active avoidance behavior (150 ppm CO), nonspatial memory (75 and 150 ppm CO), spatial learning (endogenous CO inhibition), homing behavior

(150 ppm CO), locomotor movement (150 ppm CO), and negative geotaxis (125 and 150 ppm). In two separate studies, in utero CO exposure (75 and 150 ppm) was associated with significant myelination decrements without associated changes in motor activity in adult animals. Multiple studies demonstrated that in utero CO exposure affected glutamatergic, cholinergic, catecholaminergic, and dopaminergic neurotransmitter levels or transmission. Possible or demonstrated adverse outcomes from the CO-mediated aberrant neurotransmitter levels or transmission include respiratory dysfunction (200 ppm CO), impaired sexual behavior (150 ppm CO), and an adverse response to hyperthermic insults resulting in neuronal damage (200 ppm). Finally, perinatal CO exposure has been shown to affect the developing auditory system of rodents, inducing permanent changes into adulthood. This is manifested by atrophy of cochlear cells innervating the inner hair cells (25 ppm CO), decreased immunostaining associated with impaired neuronal activation (12.5 ppm CO), impaired myelination of auditory associated nerves (25 ppm CO), decreased energy production in the sensory cell organ of the inner ear or the organ of corti (25 ppm CO). Some of these changes have been proposed to be mediated by ROS. Functional tests of the auditory system of rodents exposed neonatally to CO using OAE testing (50 ppm) and action potential amplitude measurements of the 8th cranial nerve (12, 25, 50, 100 ppm), revealed decrements in auditory function at PND22 and permanent changes into adulthood using action potential (AP) testing (50 ppm). Additionally, exposure to high concentrations of CO has been shown to result in CO-dependent ototoxicity in adult animals, possibly through glutamate and ROS-dependent mechanisms. Together, these animal studies demonstrated that in utero or perinatal exposure to CO can adversely affect adult behavior, neuronal myelination, neurotransmission, and the auditory system in adult rodents. Considering the combined evidence from controlled human exposure and toxicological studies, the evidence is **suggestive of a causal relationship between relevant short- and long-term exposures to CO and central nervous system effects.**

5.4. Birth Outcomes and Developmental Effects

5.4.1. Epidemiologic Studies

Although the body of literature is growing, the research focusing on adverse birth outcomes is limited when compared to the numerous studies that have examined the more well-established health effects of air pollution. Among this small number of studies, various dichotomized measures of birth weight, such as low birth weight (LBW), small for gestational age (SGA), and intrauterine growth restriction (IUGR), have received more attention in air pollution research while preterm birth (<37 wk gestation; [PTB]), congenital malformations, and infant mortality are less studied.

In the 2000 CO AQCD (U.S. EPA, 2000, 000907), only two studies were cited that examined the effect of ambient air pollution on adverse birth outcomes, and both of these studies investigated LBW as an endpoint (Alderman et al., 1987, 012243; Ritz and Yu, 1999, 086976). At that time this area of research was in its infancy; however, there has since been increasing interest.

5.4.1.1. Preterm Birth

A small number of air pollution-birth outcome studies have investigated the possible association between PTB and maternal exposure to CO, with the majority of U.S. studies conducted in southern California. The earliest of these studies examined exposures to ambient CO during the first month of pregnancy and the last 6 wk prior to birth among a cohort of 97,158 births in southern California between 1989 and 1993 (Ritz et al., 2000, 012068). The exposure assessment within this study was based on data from fixed-site monitors that fell within a 2-mi radius of the mother's ZIP code area. The crude relative risks for PTB associated with a 1 ppm increase in 3-h avg CO concentration (6:00-9:00 a.m.) during the last 6 wk prior to birth and the first month of pregnancy were 1.04 (95% CI: 1.03-1.5) and 1.01 (95% CI: 1.00-1.03), respectively. However, when the authors controlled for other risk factors, only the effect associated with CO during the last 6 wk prior to birth persisted (RR: 1.02 [95% CI: 1.01-1.03]). Furthermore, when the analyses included variables

for either season or other pollutants, the CO effect estimates generally were reduced such that they remained positive but were no longer statistically significant.

Expanding on this research, Wilhelm and Ritz (2005, 088668) examined PTB among a cohort of 106,483 births in Los Angeles County, CA, between 1994 and 2000. Based on data recorded at monitoring stations of varying proximities to the mother's residence, the main exposure windows examined were the first trimester and the last 6 wk prior to birth. Among women living within a 1-mi radius of a CO monitoring station, a 0.5 ppm increase in 24-h avg CO concentration during the first trimester was associated with a 3% (RR: 1.03 [95% CI: 1.00-1.06]) increased risk of PTB. This result persisted after simultaneously adjusting for NO_2 and O_3 (RR: 1.05 [95% CI: 1.00-1.10]) but not with the inclusion of PM_{10} into the regression model (RR: 0.99 [95% CI: 0.91-1.09]). The result from the single pollutant model for CO exposures averaged over the 6 wk prior to birth was similar in magnitude but failed to reach statistical significance (RR: 1.02 [95% CI: 0.99-1.04]).

A limitation of many air pollution-birth outcome studies is the limited availability of detailed information on maternal lifestyle factors and time-activity patterns during pregnancy. To assess possible residual confounding due to these factors, Ritz and colleagues (2007, 096146) were able to analyze detailed maternal information from a survey of 2,543 from a cohort of 58,316 eligible births in 2003 in Los Angeles County. Based on data from the closest monitor to the mother's ZIP code area, exposures to CO, NO_2, O_3, and $PM_{2.5}$ during the first trimester and last 6 wk prior to delivery were examined, and results from the overall cohort (n = 58,316) with limited maternal information were compared to the more detailed nested case-control cohort (n = 2,543). Within the overall cohort, 24-h avg CO during the first trimester was associated with an increased risk of 25% (OR: 1.25 [95% CI: 1.12-1.38]; highest exposure group >1.25 ppm versus lowest ≤ 0.58 ppm). This result persisted within the nested case-control cohort (OR: 1.21 [95% CI: 0.88-1.65]) where factors such as passive smoking and alcohol use during pregnancy were included in the model; however, the confidence intervals were wider due to the smaller sample. Any possible association between CO and PTB was less evident during the last 6 wk prior to birth. A strength of this study was that it also highlighted how there was little change in the air pollution effect estimates when controlling for more detailed maternal information (e.g., smoking, alcohol use), as opposed to only controlling for more limited maternal information that is routinely collected on birth registry forms.

In contrast to the Los Angeles studies, a case-control study of PTB across California for the period 1999 through 2000 found a positive association with 24-h CO concentration during the entire pregnancy (OR: 1.03 [95% CI: 0.98-1.09] per 0.5 ppm increase) and the first month of gestation (OR: 1.05 [95% CI: 0.99-1.10] per 0.5 ppm increase), but no association during the last 2 wk of gestation (OR: 1.00 [95% CI: 0.96-1.04] per 0.5 ppm increase) (Huynh et al., 2006, 091240). Although there was an indication of an effect during early pregnancy, the small sample size (when compared to other studies) may not have provided sufficient power to detect statistical significance. Furthermore, exposures within this study were assigned based on a county-level average which may explain the lack of effect, given the poor level of exposure assessment.

Studies outside of the U.S. have been conducted in Canada, Australia, and Korea, with mixed results reported. In Vancouver, Canada, based on a city-wide average across available monitoring sites, 24-h avg CO concentration during the last month of pregnancy was associated with a 4% (OR: 1.04 [95% CI: 1.00-1.07]) increased risk of PTB per 0.5 ppm increase, while there was no association found during the first month of pregnancy (OR: 0.98 [95% CI: 0.94-1.00]) (Liu et al., 2003, 089548). This study investigated maternal exposures to ambient gaseous pollutants (CO, NO_2, SO_2, O_3) averaged over the first and last month of pregnancy among a cohort of 229,085 births between 1985 and 1998.

In a cohort of 52,113 births in Incheon, Korea, between 2001 and 2002, a kriging technique was used to assign the maternal exposures to CO. Kriging is a statistical mapping technique that allows the prediction of an average concentration over a spatial region from data collected at specific points. The spatial average CO concentrations were then linked to each study subject's residential address. CO concentrations during the first trimester were associated with a 26% (RR: 1.26 [95% CI: 1.11-1.44]) increased risk of PTB for the highest quartile of exposure when compared to the lowest quartile (Leem et al., 2006, 089828). There was also a strong significant trend exhibited across the quartiles. A similar result was found for 24-h avg CO concentration during the last trimester, although the effect was less pronounced (RR: 1.16 [95% CI: 1.01-1.24]).

Conversely, a study in Sydney, Australia, examined maternal exposure to ambient air pollution during the first and last month and the first and last trimester of pregnancy among a cohort of 123,840 births between 1998 and 2000 and found no association between PTB and CO (Jalaludin et

al., 2007, 156601). Maternal exposure estimates in this study were based on a city-wide average of available monitoring sites and also based on data from fixed sites within 5 km of the mother's postcode area. The odds ratios for PTB associated with 8-h avg CO concentrations during the first trimester and last 3 mo of gestation were 1.18 (95% CI: 0.85-1.63) and 1.08 (95% CI: 0.95-1.22), respectively, when including births within 5 km of a monitor. Interestingly, when all births were included in the analyses and the exposure was based on a city-wide average, these effects had become protective for the first trimester (OR: 0.82 [95% CI: 0.77-0.87]) and null for the last 3 mo of gestation (OR: 0.99 [95% CI: 0.92-1.07]). This suggests that exposures based on data from fixed sites closer to the mother's address are more likely to detect an effect than a city-wide average.

Figure 5-9 shows the odds for the risk of delivering a preterm infant from the reviewed studies; Table 5-12 provides a brief overview of the PTB studies. In summary, there are mixed results across the studies. Although these studies are difficult to compare directly due to the different exposure assessment methods employed, there is some evidence that CO during early pregnancy (e.g., first month and trimester) is associated with an increased risk of PTB. The most consistency is exhibited within the studies conducted around Los Angeles, CA, and surrounding areas, whereby all studies reported a significant association with CO exposure during early pregnancy, and exposures were assigned from monitors within close proximity of the mother's residential address (Ritz et al., 2000, 012068; Ritz et al., 2007, 096146; Wilhelm and Ritz, 2005, 088668). It should also be noted that the mixed results when analyzing different cohorts that resided within varying proximities to a monitor may be attributable to analyzing different populations.

Study	Location	Exposure Period	Exposure Indicator
Ritz et al. (2000, 012068)	California, US	First month	<2 mi of monitor
Ritz et al. (2000, 012068)	California, US	Last 6 weeks	<2 mi of monitor
Wilhelm & Ritz (2005, 088668)	Los Angeles, CA	First trimester	ZIP code level
Wilhelm & Ritz (2005, 088668)	Los Angeles, CA	Last 6 weeks	ZIP code level
Huynh et al. (2006, 091240)	California, US	First month	County level
Huynh et al. (2006, 091240)	California, US	Last 2 weeks	County level
Huynh et al. (2006, 091240)	California, US	Entire pregnancy	County level
Liu et al. (2003, 089548)	Vancouver, Can	First month	City wide
Liu et al. (2003, 089548)	Vancouver, Can	Last month	City wide
Jalaludin et al. (2007, 156601)	Sydney, Australia	First month	City wide
Jalaludin et al. (2007, 156601)	Sydney, Australia	First trimester	City wide
Jalaludin et al. (2007, 156601)	Sydney, Australia	Last month	City wide

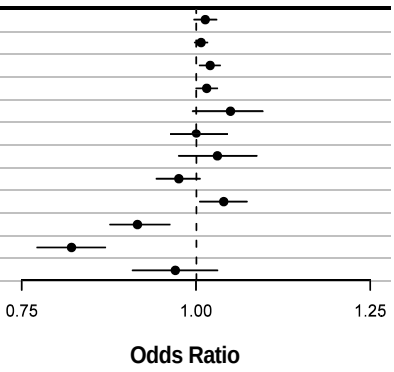


Figure 5-9. Summary of effect estimates (95% confidence intervals) for PTB associated with maternal exposure to ambient CO. Effect estimates have been standardized to a 1 ppm increase in ambient CO for 1-h max CO concentrations, 0.75 ppm for 8-h max CO concentrations, and 0.5 ppm for 24-h avg CO concentrations.

Table 5-12. Brief summary of PTB studies.

Study	Location Sample Size	Mean CO (ppm)	Exposure Assessment	Exposure Window
Ritz et al. (2000, 012068)	California, US (n = 97,158)	2.7 (6-9 a.m.)	<2 mi of monitor	First mo Last 6 wk
Wilhelm and Ritz (2005, 088668)	Los Angeles, CA (n = 106,483)	1.4 (24 h)	Varying distances to monitor	Last 6 wk
Ritz et al.(2007, 096146)	Los Angeles, CA (n = 58,316)	0.87 (24 h)	Nearest monitor to ZIP code	Entire pregnancy First Trimester Last 6 wk
Huynh et al. (2006, 091240)	California, US (n = 42,692)	0.8 (24 h)	County level	Entire pregnancy First mo Last 2 wk
Liu et al. (2003, 089548)	Vancouver, Can (n = 229,085)	1.0 (24 h)	City-wide avg	First mo Last mo
Leem et al. (2006, 089828)	Incheon, Korea (n = 52,113)	0.9 (24 h)	Residential address within Dong-based on kriging	First trimester Last trimester
Jalaludin et al. (2007, 156601)	Sydney, Australia (n = 123,840)	0.9 (8 h)	City-wide avg and <5 km from monitor	First mo First trimester Last trimester Last mo

5.4.1.2. Birth Weight, Low Birth Weight, and Intrauterine Growth Restriction/Small for Gestational Age

With birth weight routinely collected in vital statistics and being a powerful predictor of infant mortality, it is the most studied outcome within air pollution-birth outcome research. Air pollution researchers have analyzed birth weight as a continuous variable and/or as a dichotomized variable in the forms of LBW (<2,500 g [5 lbs, 8 oz]) and SGA.

It should be noted that the terms SGA, which is defined as a birth weight <10th percentile for gestational age (and often sex), and IUGR are used interchangeably. However, this definition of SGA does have limitations. For example, using it for IUGR may overestimate the percentage of "growth-restricted" neonates as it is unlikely that 10% of neonates have growth restriction (Wollmann, 1998, 193812). On the other hand, when the 10th percentile is based on the distribution of live births at a population level, the percentage of SGA among preterm births is most likely underestimated (Hutcheon and Platt, 2008, 193795). Nevertheless, it should be noted that SGA represents a statistical description of a small neonate, whereas the term IUGR is reserved for those with clinical evidence of abnormal growth. Thus, all IUGR neonates will be SGA, but not all SGA neonates will be IUGR (Wollmann, 1998, 193812). In the following sections the terms SGA and IUGR are referred to as each cited study used the terms.

Over the past decade a number of studies examined various metrics of birth weight in relation to maternal exposure to CO with the majority conducted in the U.S. Given that most studies examined multiple birth weight metrics, the following section focuses on each study only once and presents results for each metric within that study.

Most of the U.S. studies have been conducted in southern California, with inconsistent results reported with regard to gestational timing of the CO effects. The first of these studies was reviewed in the 2000 CO AQCD (U.S. EPA, 2000, 000907) and is briefly summarized here. Ritz and Yu (1999, 086976) examined the effect of ambient CO during the last trimester on LBW among 125,573 births in Los Angeles between 1989 and 1993. When compared to neonates born to women in the lowest CO exposure group (<2.2 ppm), neonates born to women in the highest exposure group (5.5 ppm-95th percentile) had a 22% (OR: 1.22 [95% CI: 1.03-1.44]) increased risk of being born as LBW.

Building upon this research, Wilhelm and Ritz (2005, 088668) reported similar results when extending this study to include 136,134 births for the period 1994–2000. Exposure to ambient CO

during each trimester was based on data recorded at monitoring stations of varying proximities to the mother's residence. For women residing within 1 mi of a station, there was 36% (OR: 1.36 [95% CI: 1.04-1.76]) increased risk of having a term LBW baby for women with third-trimester exposure above the 75th percentile when compared to women below the 75th percentile. There was also an increased risk of term LBW (OR: 1.28 [95% CI: 1.12-1.47]) among women in the highest exposure group when the analyses included women within a 5-mi radius of a station. However, when the analyses included women within a 1- to 2-mi or 2- to 4-mi radius of a station, the CO effects failed to reach statistical significance, and there was no evidence of an exposure-response pattern exhibited across the varying distances to a station. Furthermore, none of the significant CO results persisted after controlling for other pollutants. Although standard errors were certainly increased after controlling for the other pollutants, leading to non-significant results, some of the effect sizes were similar, providing some consistency. It is interesting to note, however, that maternal exposure to CO during trimesters one and two was not associated with LBW (quantitative results not reported by authors).

Further validation in association with exposure times was observed in an analysis using a subset of participants in the Children's Health Study. Salam and colleagues (2005, 087885) found that CO only during the first trimester was associated with reduced fetal growth. Their research examined birth weight, LBW, and IUGR among a subset of participants in the Children's Health Study (Peters et al., 1999, 087243) who were born in California between 1975 and 1987 (n = 3,901). The study examined term births with a gestational age between 37 and 44 wk. Exposures in this study were based on CO data from up to the 3 nearest monitoring sites within 50 km of the centroid of the mother's ZIP code. Exposures for the entire pregnancy and each trimester were analyzed, and a 0.5 ppm increase in 24-h CO concentration during the first trimester was associated with a 7.8 g (95% CI: 15.1-0.4) decrease in birth weight, which also translated to a 6.7% (OR: 1.07 [95% CI: 1.00-1.13]) increased risk of IUGR; however, there was no association with LBW (OR: 1.00 [95% CI: 0.88-1.16]).

In contrast to the previous studies, another California study of 18,247 singleton births born at 40-wk gestation during 2000 found no association between ambient 24-h CO concentration and reduced birth weight or SGA, where the highest quartile of exposure was 0.98 ppm. Based on data from fixed sites within 5 mi of the mother's residence, exposures to CO and $PM_{2.5}$ during the entire pregnancy and each trimester were analyzed. Although CO during the entire pregnancy was associated with a 20 g (95% CI: 40.1-0.8) reduction in birth weight, this did not persist after controlling for $PM_{2.5}$. $PM_{2.5}$ was found to have a strong effect on birth weight within each trimester (Parker et al., 2005, 087462).

Two similar studies were conducted in the northeastern U.S. with inconsistent results. A study of 89,557 singleton term births in Boston, MA, Hartford, CT, Philadelphia, PA, Pittsburgh, PA, and Washington, DC, between 1994 and 1996 found that exposure to ambient 24-h avg CO during the third trimester was associated with an increased risk of LBW (OR: 1.14 [95% CI: 1.03-1.27] per 0.5 ppm increase) (Maisonet et al., 2001, 016624). When stratified by race this effect was only significant among African-Americans for the first and third trimesters (first OR: 1.32 [95% CI: 1.22-1.43]; third OR: 1.20 [95% CI: 1.09-1.32]). Exposures to PM_{10} and SO_2 were examined, and there was no strong evidence that these pollutants were associated with LBW. Exposures for this study were based on a city-wide average of monitors within the mother's city of residence. The second study examined 358,504 births at 32- to 44-wk gestation between 1999 and 2002 in Connecticut and Massachusetts (Bell et al., 2007, 091059), and 24-h CO exposures were estimated from fixed sites within each mother's county of residence (e.g., county level). CO averaged over the entire pregnancy was associated with a reduction in birth weight of 27.0 g (95% CI: 21.0-32.8). This result persisted after controlling for each additional pollutant (PM_{10}, $PM_{2.5}$, NO_2, and SO_2) in two-pollutant models. However, this reduction in birth weight did not translate to an increased risk of LBW (OR: 1.05 [95% CI: 0.97-1.12] per 0.5 ppm increase in CO). When controlling for exposure during each trimester, the reduction in birth weight associated with a 0.5 ppm increase in 24-h CO concentration during the first trimester ranged from 18.8 to 16.5 g, while the reductions associated with third trimester exposure ranged between 27.2 and 23.3 g. It is interesting to note that, although the exposures were based on data averaged at the county level, CO was associated with a reduction in birth weight. In contrast, in a previously cited California study by Huynh and colleagues (2006, 091240) exposures were also at the county level yet there was no association with PTB. This difference may be due to the counties being smaller in New England than in California, resulting in more precise exposure estimates.

Two studies in Canada investigated the effects of ambient air pollution on fetal growth with exposures derived from a city-wide average across the available monitoring sites. The first of these studies was among a cohort of 229,085 singleton term births (37- and 42-wk gestation) in Vancouver, BC, with monthly and trimester exposures to CO investigated in relation to LBW and IUGR (Liu et al., 2003, 089548). For a 0.5 ppm increase in 24-h CO concentration during the first month of pregnancy, there was an increased risk of IUGR (OR: 1.03 [95% CI: 1.00-1.05]), and this was of borderline significance when CO was averaged over the first trimester (OR: 1.02 [95% CI: 1.00-1.05]). This result persisted after controlling for other gaseous pollutants. Conversely, maternal exposure to CO was not associated with LBW. The more recent of these two studies examined 386,202 singleton term births (37- to 42-wk gestation) in Calgary, Edmonton, and Montreal, between 1986 and 2000 (Liu et al., 2007, 090429). The study examined monthly and trimester exposures to CO with IUGR being the only endpoint. A 0.5 ppm increase in 24-h CO concentration was associated with an increased risk of IUGR in the first (OR: 1.09 [95% CI: 1.07-1.11]), second (OR: 1.07 [95% CI: 1.05-1.09]), and third trimesters (OR: 1.09 [95% CI: 1.07-1.11]) of pregnancy. This result translated to CO exposure having a positive effect on IUGR within each individual month of pregnancy with the highest effect during the first and last months. This result persisted after controlling for concurrent NO_2 and $PM_{2.5}$.

Two studies in Sao Paulo, Brazil, a city with notably high levels of air pollution (mean CO 3.7 ppm) investigated associations between maternal exposures to CO in relation to reduced birth weight and LBW within two consecutive time periods and found similar results. In both studies the exposures were derived from a city-wide average across the available monitoring sites. The first study examined 179,460 singleton term births during 1997 and found that a 0.75 ppm increase in 8-h CO concentration averaged over the first trimester was associated with a 17.3 g (95% CI: 31.0-3.7) reduction in birth weight (Gouveia et al., 2004, 055613). The second of these studies examined 311,735 singleton births (37- to 41-wk gestation) between 1998 and 2000 and reported a 6.0 g (95 % CI: 7.75-4.1) reduction in birth weight associated with a 0.5 ppm increase in 24-h CO concentration averaged over the first trimester (Medeiros and Gouveia, 2005, 089824). It is important to note that neither of these studies found an association between CO exposure and an increased risk of LBW. Therefore, despite CO during the first trimester being associated with reduced birth weight, it was not associated with LBW.

Similar to the two studies in Sao Paulo, Brazil, researchers in Seoul, South Korea, conducted two studies using data from two consecutive time periods. Both of these studies based the exposure estimates on a city-wide average from all available fixed sites and as would be expected, the results pertaining to CO were similar for both studies. Ha and colleagues (2001, 019390) examined maternal exposures to CO during the first and third trimesters among 276,763 singleton term births in Seoul between 1996 and 1997. Exposure to CO during the first trimester was associated with a decrease in birth weight of 13.3 g, which also translated into an increased risk of LBW (RR: 1.10 [95% CI: 1.05-1.14] per 0.5 ppm increase in 24-h CO concentration). When Lee and colleagues (2003, 043202) extended this study to include singleton term births for the period 1996-1998, with 24-h CO concentrations averaged over each month of pregnancy and trimester, CO exposure during the first trimester was associated with an increased risk of LBW (OR: 1.04 [95% CI: 1.01-1.07] per 0.5 ppm increase). No associations were found in the third trimester for any of the pollutants. Monthly-specific exposures showed that the risk of LBW tended to increase with CO exposure between months two through five of pregnancy.

In contrast to other studies reporting that early and late pregnancy are the critical periods for CO exposure, a Sydney, Australia study of 138,056 singleton births between 1998 and 2000 reported a reduction in birth weight of 21.7 g (95% CI: 38.2-5.1) and 17.2 g (95% CI: 33.4-0.9) associated with a 0.75 ppm increase in maternal exposure to 8-h CO averaged over the second and third trimesters, respectively (Mannes et al., 2005, 087895). However, this result did not persist after controlling for other pollutants (PM_{10}, NO_2) and was only statistically significant when including births where the mother resided within 5 km of a monitor. Furthermore, this result did not translate to an increased risk of SGA, which was defined as a birth weight two standard deviations below the mean. The odds ratios for SGA for CO exposures during the first, second and third trimesters were 0.96 (95% CI: 0.91-1.03), 0.99 (95% CI: 0.92-1.07), and 1.01 (95% CI: 0.93-1.08) per 0.75 ppm increase in 8-h CO, respectively. While the majority of studies restrict the analyses to term births as a method of controlling for gestational age, it is important to note that the Sydney study used all births and controlled for gestational age in the birth weight analyses and SGA was derived for each gestational age group.

Of all studies reviewed, only two did not find an association between maternal exposure to CO and birth weight variables. In northern Nevada, Chen and colleagues (2002, 024945) examined CO, PM_{10}, and O_3 exposures among a cohort of 39,338 term births (37- to 44-wk gestation) between 1991 and 1999 and found no association between CO exposure during the entire pregnancy (and each trimester) and a reduction in birth weigh or an increased risk of LBW. For a 0.75 ppm increase in 8-h CO concentration averaged over the entire pregnancy, there was a reduction in birth weight of 6 g; however it failed to reach statistical significance. Exposures for this study were based on data from all monitoring sites across Washoe County, Nevada.

In a retrospective cohort study among 92,288 singleton term births (37- to 44-wk gestation) in Taipei and Kaoshiung, Taiwan, between 1995 and 1997, maternal exposures to CO, SO_2, O_3, NO_2, and PM_{10} in each trimester of pregnancy were examined, and only SO_2 during the third trimester showed evidence of contributing to LBW. Exposure assessment was based on data from the monitor closest to the centroid of the mother's residential district, and the final analyses included only those mothers whose district centroid was within 3 km of a monitor. CO exposures were grouped into low (~1.1 ppm), medium (~1.2-15.0 ppm), and high (>15.0 ppm) and when compared to the lowest exposure group, the odds ratio for LBW in the highest exposure group was 0.90 (95% CI: 0.75-1.09) for the first trimester, 1.00 (95% CI: 0.82-1.22) for the second trimester, and 0.86 (95% CI: 0.71-1.03) for the third trimester (Lin et al., 2004, 089827).

Table 5-13 provides a brief overview of the birth weight studies. In summary, there is evidence of ambient CO during pregnancy having a negative effect on fetal growth. From the reviewed studies Figure 5-10 shows the change in birth weight (grams), Figure 5-11 shows the effect estimates for LBW, and Figure 5-12 shows the effect estimates for SGA. In general the reported reductions in birth weight are small (~10-20g). It is difficult to conclude whether CO is related to a small change in birth weight in all births across the population or a marked effect in some subset of births. Furthermore, there is a large degree of inconsistency across these studies. This may be due to several factors such as inconsistent exposure assessment and statistical methods employed, different CO concentrations, and/or different demographics of the birth cohorts analyzed. The main inconsistency among these findings is the gestational timing of the CO effect. Although the majority of studies reported significant effects during either the first or third trimester, other studies failed to find a significant effect during these periods. Several studies found an association with exposure during the entire pregnancy, providing evidence for a possible accumulative effect; however, these results are inconclusive and may be the result of correlated exposure periods.

Several studies examined various combinations of birth weight, LBW, and SGA/IUGR, and inconsistent results are reported across these metrics. For example, several studies reported an association between maternal exposure to CO and decreased birth weight, yet no increase in risk of LBW or SGA. However, a measurable change, even if only a small one, at the population level is different than an effect observed for a subset of susceptible births which may increase the risk of IUGR/LBW/SGA. It is difficult to conclude if CO is related to a small change in birth weight in all births across the population or a marked effect in some subset of births.

Study	Location	Exposure Period	Exposure Indicator
Bell et al. (2007, 091059)	CT & MA, US	Entire pregnancy	County wide
Salam et al. (2005, 087885)	California, US	First trimester	ZIP code level
Salam et al. (2005, 087885)	California, US	Second trimester	ZIP code level
Salam et al. (2005, 087885)	California, US	Third trimester	ZIP code level
Salam et al. (2005, 087885)	California, US	Entire pregnancy	ZIP code level
Chen et al. (2002, 024945)	Northern NV, US	First trimester	County level
Chen et al. (2002, 024945)	Northern NV, US	Second trimester	County level
Chen et al. (2002, 024945)	Northern NV, US	Third trimester	County level
Chen et al. (2002, 024945)	Northern NV, US	Entire pregnancy	County level
Mannes et al. (2005, 087895)	Sydney, Australia	First trimester	City level
Mannes et al. (2005, 087895)	Sydney, Australia	Second trimester	City level
Mannes et al. (2005, 087895)	Sydney, Australia	Third trimester	City level
Mannes et al. (2005, 087895)	Sydney, Australia	Last month	City level
Gouveia et al. (2004, 055613)	Sao Paulo, Brazil	First trimester	City level
Gouveia et al. (2004, 055613)	Sao Paulo, Brazil	Second trimester	City level
Gouveia et al. (2004, 055613)	Sao Paulo, Brazil	Third trimester	City level
Medeiros and Gouveia (2005, 089824)	Sao Paulo, Brazil	First trimester	City level
Medeiros and Gouveia (2005, 089824)	Sao Paulo, Brazil	Second trimester	City level
Medeiros and Gouveia (2005, 089824)	Sao Paulo, Brazil	Third trimester	City level

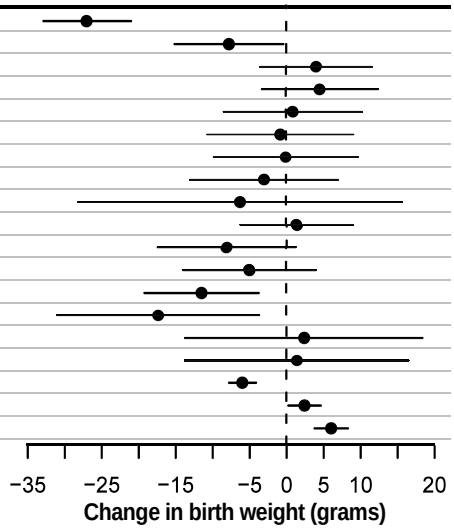


Figure 5-10. Summary of change in birth weight (95% confidence intervals) associated with maternal exposure to ambient CO. Effect estimates have been standardized to a 1 ppm increase in ambient CO for 1-h max CO concentrations, 0.75 ppm for 8-h max CO concentrations, and 0.5 ppm for 24-h avg CO concentrations.

Study	Location	Exposure Period	Exposure Indicator
Bell et al. (2007, 091059)	CT & MA, US	Entire pregnancy	County level
Maisonet et al. (2001, 016624)	Northeastern US	First trimester	City level
Maisonet et al. (2001, 016624)	Northeastern US	Second trimester	City level
Maisonet et al. (2001, 016624)	Northeastern US	Third trimester	City level
Wilhelm & Ritz (2005, 088668)	LA County, CA	Third trimester	ZIP code level
Salam et al. (2005, 087885)	California, US	First trimester	ZIP code level
Salam et al. (2005, 087885)	California, US	Second trimester	ZIP code level
Salam et al. (2005, 087885)	California, US	Third trimester	ZIP code level
Salam et al. (2005, 087885)	California, US	Entire pregnancy	ZIP code level
Liu et al. (2003, 089548)	Vancouver, Can	First month	City level
Liu et al. (2003, 089548)	Vancouver, Can	Second month	City level
Ha et al. (2001, 019390)	Seoul, Korea	First trimester	City level
Ha et al. (2001, 019390)	Seoul, Korea	Third trimester	City level
Lee et al. (2003, 043202)	Seoul, Korea	First trimester	City level
Lee et al. (2003, 043202)	Seoul, Korea	Second trimester	City level
Lee et al. (2003, 043202)	Seoul, Korea	Third trimester	City level
Lee et al. (2003, 043202)	Seoul, Korea	Entire pregnancy	City level

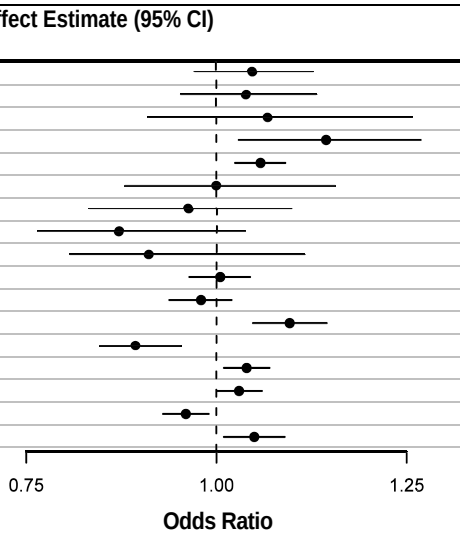


Figure 5-11. Summary of effect estimates (95% confidence intervals) for LBW associated with maternal exposure to ambient CO. Effect estimates have been standardized to a 1 ppm increase in ambient CO for 1-h max CO concentrations, 0.75 ppm for 8-h max CO concentrations, and 0.5 ppm for 24-h avg CO concentrations.

Study	Location	Exposure Period	Exposure Indicator	Effect Estimate (95% CI)
Salam et al. (2005, 087885)	California, US	First trimester	ZIP code level	
Salam et al. (2005, 087885)	California, US	Second trimester	ZIP code level	
Salam et al. (2005, 087885)	California, US	Third trimester	ZIP code level	
Salam et al. (2005, 087885)	California, US	Entire pregnancy	ZIP code level	
Liu et al. (2003, 089548)	Vancouver, Can	First month	City level	
Liu et al. (2003, 089548)	Vancouver, Can	First trimester	City level	
Liu et al. (2003, 089548)	Vancouver, Can	Second trimester	City level	
Liu et al. (2003, 089548)	Vancouver, Can	Third trimester	City level	
Liu et al. (2003, 089548)	Vancouver, Can	Last month	City level	
Liu et al. (2007, 090429)	Multicity, Can	First trimester	City level	
Liu et al. (2007, 090429)	Multicity, Can	Second trimester	City level	
Liu et al. (2007, 090429)	Multicity, Can	Third trimester	City level	
Mannes et al. (2005, 087895)	Sydney, Australia	First trimester	City level	
Mannes et al. (2005, 087895)	Sydney, Australia	Second trimester	City level	
Mannes et al. (2005, 087895)	Sydney, Australia	Third trimester	City level	
Mannes et al. (2005, 087895)	Sydney, Australia	Last month	City level	

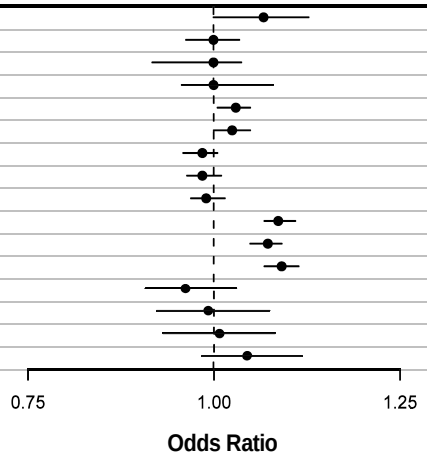


Figure 5-12. Summary of effect estimates (95% confidence intervals) for SGA associated with maternal exposure to ambient CO. Effect estimates have been standardized to a 1 ppm increase in ambient CO for 1-h max CO concentrations, 0.75 ppm for 8-h max CO concentrations, and 0.5 ppm for 24-h avg CO concentrations.

The possibility exists that the small reductions in birth weight associated with maternal CO exposures are the result of residual confounding associated with other factors (e.g., other pollutants, temperature, and spatial/temporal variation in maternal factors) or other correlated pollutants. For example, in some studies the CO effect did not persist after controlling for other pollutants (Mannes et al., 2005, 087895; Parker et al., 2005, 087462; Wilhelm and Ritz, 2005, 088668), while in some studies it did persist (Bell et al., 2007, 091059; Gouveia et al., 2004, 055613; Liu et al., 2003, 089548), and other studies did not report results from multipollutant models (Ha et al., 2001, 019390; Lee et al., 2003, 043202; Maisonet et al., 2001, 016624; Medeiros and Gouveia, 2005, 089824). In addition, various methods have been employed to control for seasonality and trends (e.g., month of birth, season of birth, year of birth, smoothed function of time), which may explain some of the mixed results.

The two U.S. studies conducted in the Northeast compared results from analyses stratified by race. The earlier of these studies found an association between CO and LBW among African-Americans but not among whites and Hispanics (Maisonet et al., 2001, 016624). In contrast, despite reporting an 11g reduction in birth weight among African-Americans and a 17 g reduction among whites, the more recent of the two studies found no significant difference between these reductions by race (Bell et al., 2007, 091059). Parker and colleagues (2005, 087462) also tested for interactions between race and found no significant association.

Table 5-13. Brief summary of birth weight studies.

Study	Outcomes Examined	Location Sample Size	Mean CO (ppm)	Exposure Assessment	Exposure Windows
UNITED STATES					
Ritz and Yu (1999, 086976)	LBW	Los Angeles, CA (n = 125, 573)	2.6 (6-9 a.m.)	<2 mi of monitor	Trimester 3
Wilhelm and Ritz (2005, 088668)	LBW	Los Angeles County, CA (n = 136, 134)	1.4 (24 h)	Varying distances from monitor	Trimesters 1, 2, 3
Salam et al. (2005, 087885)	Birth weight LBW IUGR	California, US (n = 3901)	1.8 (24 h)	ZIP code level	Entire pregnancy Trimesters 1, 2, 3
Parker et al. (2005, 087462)	Birth weight SGA	California, US (n = 18,247)	0.75 (8 h)	<5 mi from monitor	Entire pregnancy Trimesters 1, 2, 3
Maisonet et al. (2001, 016624)	LBW	Boston, MA Hartford, CT Philadelphia & Pittsburg, PA Washington DC (n = 103,465)	1.1 (24 h)	City-wide avg	Trimesters 1, 2, 3
Bell et al. (2007, 091059)	Birth weight LBW	CT & MA, US (n = 358,504)	0.6 (24 h)	County-level avg	Entire pregnancy Trimesters 1, 3
Chen et al. (2002, 024945)	Birth weight LBW	Northern Nevada, US (n = 36,305)	0.9 (8 h)	County level	Trimesters 1, 2, 3
CANADA					
Liu et al. (2003, 089548)	LBW IUGR	Vancouver, Can (n = 229,085)	1.0 (24 h)	City-wide avg	Trimester 1
Liu et al. (2007, 090429)	IUGR	Calgary, Edmonton, & Montreal, Can (n = 386,202)	1.1 (24 h)	City-wide avg	Trimesters 1, 2, 3
SOUTH AMERICA					
Gouveia et al. (2004, 055613)	Birth weight LBW	Sao Paulo, Brazil (n = 179,460)	3.7 (8 h)	City-wide avg	Trimesters 1, 2, 3
Medeiros and Gouveia (2005, 089824)	Birth weight LBW	Sao Paulo, Brazil (n = 311,735)	3.0 (24 h) (Presented in graph)	City-wide avg	Trimesters 1, 2, 3
AUSTRALIA/ASIA					
Ha et al. (2001, 019390)	Birth weight LBW	Seoul, Korea (n = 276,763)	1.2 (24 h)	City-wide avg	Trimesters 1 and 3
Lee et al. (2003, 043202)	LBW	Seoul, Korea (n = 388,105)	1.2 (24 h)	City-wide avg	Entire pregnancy Trimesters 1, 2, 3
Mannes et al. (2005, 087895)	Birth weight SGA	Sydney, Australia (n = 138,056)	0.8 (8 h)	City-wide avg and <5 km from monitor	Trimesters 1, 2, 3 Last 30 days
Lin et al. (2004, 089827)	LBW	Taipei, Kaoshiung, Taiwan (n = 92,288)	Taipei 1.1, Kaoshiung 8.1	<3 km of monitor	Entire pregnancy Trimesters 1, 2, 3

5.4.1.3. Congenital Anomalies

Despite the growing evidence of an association between ambient air pollution and various adverse birth outcomes, few studies have investigated the effect of temporal variations in ambient air pollution on congenital anomalies. Heart defects have been the focus of the majority of these recent air pollution studies, given the higher prevalence than other congenital anomalies and associated mortality. Another study's focus was cleft lip/palate.

The earliest of these studies was conducted in southern California (Ritz et al., 2002, 023227). Exposure to ambient CO, NO_2, O_3 and PM_{10} during each of the first 3 mo of pregnancy was examined among births during 1987-1993. Maternal exposure estimates were based on data from the fixed site closest to the mother's ZIP code area. When using a case-control design where cases were matched to 10 randomly selected controls, results showed that CO during the second month of pregnancy was associated with cardiac ventricular septal defects. The CO exposures were grouped by quartiles (25th = 1.14, 50th = 1.57, 75th = 2.39 ppm), and when compared to those in the lowest quartile exposure group (<1.14 ppm), the odds ratios for ventricular septal defects across the 3 higher exposure groups were 1.62 (95% CI: 1.05-2.48), 2.09 (95% CI: 1.19-3.67), and 2.95 (95% CI: 1.44-6.05), respectively. In a multipollutant model a similar exposure-response pattern was exhibited across the quartiles with the highest quartile of exposure reaching statistical significance (OR: 2.84 [95% CI: 1.15-6.99]). The only other pollutant associated with a defect was O_3 during the second month of pregnancy, which was associated with aortic artery and valve defects.

Another study was conducted in Texas (Gilboa et al., 2005, 087892), where exposure to ambient CO, NO_2, SO_2, O_3 and PM_{10} during the 3rd-8th week of gestation was examined among births between 1997 and 2000. Maternal exposure estimates were calculated by assigning the data from the closest monitor to the mother's residential address. If data were missing on a particular day then data from the next closest site were used. The median distances from a monitor ranged from 8.6 to 14.2 km, with maximum distances ranging from 35.5 to 54.5 km. The main results showed that CO was associated with multiple conotruncal defects and Tetralogy of Fallot. CO exposures were grouped into quartiles of much lower concentrations (25th = 0.4, 50th = 0.5, 75th = 0.7 ppm) than the California study (Ritz et al., 2002, 023227), and when compared to the lowest quartile, the odds ratios for conotruncal defects across the 3 CO exposure groups were 1.38 (95% CI: 0.97-1.97), 1.17 (95% CI: 0.81-1.70), and 1.46 (1.03-2.08), respectively, without a significant test for trend (p for trend = 0.0870). A strong exposure-response pattern was exhibited across the quartiles of CO exposure for Tetralogy of Fallot (25th OR: 0.82 [95% CI: 0.52-1.62]; 50th OR: 1.27 [95% CI: 0.75-2.14]; 75th OR: 2.04 [95% CI: 1.26-3.29]; p for trend = 0.0017). The only significant associations found with other pollutants were between PM_{10} and isolated atrial septal defects, and SO_2 and ventricular septal defects.

A study conducted in Atlanta, GA, investigated the associations between ambient air pollution concentrations during weeks 3-7 of pregnancy and risks of cardiovascular malformations among a cohort of pregnancies conceived during 1986-2003 (Strickland et al., 2009, 190324). The mean 24-h CO concentration during this period was 0.75 ppm. The authors did not report any statistically significant associations with ambient CO concentrations and cardiac malformations, though there were elevated risk ratios for ambient CO concentration and patent ductus arteriosus, Tetralogy of Fallot, and right ventricular outflow tract defect. These results remained consistently positive in five sensitivity analyses conducted and were closer to achieving statistical significance in these sensitivity analyses. The only statistically significant results were for the association between PM_{10} and patent ductus arteriosus.

The last of these studies was a case-control study that examined maternal exposure to various air pollutants during the first 3 mo of pregnancy and the risk of delivering an infant with an oral cleft, namely cleft lip with or without palate (CL/P). Birth data from the Taiwanese birth registry from 2001 to 2003 was linked to air pollutant data that were spatially interpolated from all fixed monitoring sites across Taiwan. Based on data at the center of the townships or districts, exposure estimates for PM_{10}, SO_2, NO_X, O_3, and CO were averaged over each of the first 3 mo of pregnancy. The mean 8-h avg CO concentration was 0.69 ppm. Interestingly, of all the pollutants examined, only O_3 during the first 2 mo of pregnancy was significantly associated with an increased risk of CL/P. In multipollutant models CO was not associated with CL/P (Hwang and Jaakkola, 2008, 193794).

The main results from the southern California study showed that CO was associated with an increased risk of ventricular septal defects, and this was exhibited by an exposure-response pattern across the quartiles of exposure; yet there was no indication that ambient CO concentration in Texas

was associated with ventricular septal defects. Conversely, ambient CO concentration in Texas was associated with an increased risk of conotruncal defects; yet there was no indication that CO in southern California was associated with conotruncal defects. The Atlanta study (Strickland et al., 2009, 190324) found positive, though not statistically significant associations for patent ductus arteriosus, Tetralogy of Fallot, and right ventricular outflow tract defect. The elevated risk ratio for Tetralogy of Fallot is consistent with the result observed in Texas (Gilboa et al., 2005, 087892).

Interestingly, similar inconsistencies were also found for PM_{10} between these studies. For example, PM_{10} in Texas was associated with an increased risk of atrial septal defects and with patent ductus arteriosus in Atlanta, GA; yet there was no indication of such an effect in southern California where PM_{10} concentrations were markedly higher.

The authors of the Texas study (Gilboa et al., 2005, 087892) provided little discussion toward the inconsistent results with the southern California study. One suggestion was the different CO concentrations across the studies with the 75th quartile in southern California being 2.39 ppm while in Texas it was much lower at 0.7 ppm. However, this suggests that different defects are associated with different concentrations of CO; yet it still does not explain why particular associations were reported in Texas and not southern California where concentrations were higher. Similarly, the authors of the Texas study (Gilboa et al., 2005, 087892) also suggested the inconsistency was due to different exposure periods. In Texas the exposures were averaged over the 3rd-8th wk while in southern California the exposures were averaged over the second month of pregnancy. However, there was no reason provided as to why this small difference in the examined exposure period would explain the inconsistent results.

Overall, there is some evidence that maternal exposure to CO is associated with an increased risk of congenital anomalies, namely heart defects and cleft lip and palate. Further research is required to corroborate these findings.

5.4.1.4. Neonatal and Postneonatal Mortality

A handful of studies examined the effect of ambient air pollution on neonatal and postneonatal mortality, with the former the least studied. These studies varied somewhat with regard to the outcomes and exposure periods examined and study designs employed.

Neonatal

In Sao Paulo, Brazil, a time-series study examined daily counts of neonatal (up to 28 days after birth) deaths for the period 1998-2000 in association with concurrent-day exposure to SO_2, CO, O_3, and PM_{10}. Moving averages from 27 days were examined. The mean city-wide CO concentration was 2.8 ppm, and there was no association between daily ambient CO and neonatal deaths. Despite CO being correlated with PM_{10} ($r = 0.71$) and SO_2 ($r = 0.55$), only PM_{10} and SO_2 were associated with an increase in the daily rate of neonatal deaths (Lin et al., 2004, 095787).

In another study of neonatal death, Hajat et al. (2007, 093276) created a daily time-series of air pollution and all infant deaths between 1990 and 2000 in 10 major cities in England. The mean daily CO concentration across the 10 cites was 0.57 ppm. This study provided no evidence for an association between ambient CO concentration and neonatal deaths.

Postneonatal

Two studies in the U.S. examined the potential association between ambient CO and postneonatal (from 28 days to 1 yr after birth) mortality and inconsistent results were reported. These studies, however, varied somewhat in study design.

The first of these studies employed a case-control design and examined all infant deaths during the first year of life among infants born alive during 1989-2000 within 16 km of a monitoring site within the South Coast Air Basin of California. Exposures for 2-wk, 1-mo, 2-mo, and 6-mo periods before death were linked to each individual death. Extensive analyses were conducted for all-cause infant deaths, respiratory causes of death, and sudden infant death syndrome (SIDS). Given the long time period of the data analyzed, in order to alleviate the confounding trends in infant mortality and CO levels, this study was able to match by year (Ritz et al., 2006, 089819). Ambient

1-h max CO concentrations averaged over the 2 mo before death were associated with an 11% (OR: 1.11 [95% CI: 1.06-1.16]) increase in risk of all-cause post-neonatal death (per 1 ppm increase) and a 19% (OR: 1.19 [95% CI: 1.10-1.28]) increase in risk of SIDS. In the multipollutant models (including PM_{10}, NO_2, O_3) the positive CO mortality effect decreased by around 50% and was not statistically significant. Based on exposure from 2 wk before death, CO was associated with an increased risk of respiratory related postneonatal deaths occurring 28 days to 1 yr after birth (OR: 1.14 [95% CI: 1.03-1.25] per 1 ppm increase) and 28 days to 3 mo after birth (OR: 1.20 [95% CI: 1.02-1.40]); but no effect was observed for respiratory related deaths occurring 4-12 mo after birth. These results persisted in the multipollutant models, and exposure-response patterns were exhibited across the exposures groupings of 1.02 to <2.08, and ≥ 2.08 ppm. To control for gestational age and birth weight the analyses were stratified by "term/normal-weight infants" and "preterm and/or LBW infants." When these two strata were analyzed, CO was associated with an increased risk of all-cause death and SIDS within both strata (ORs ranged from 1.12 to 1.46). However, these effects did not persist in multipollutant models (Ritz et al., 2006, 089819).

Another study examined 3,583,495 births, including 6,639 postneonatal deaths occurring in 96 counties throughout the U.S. (in counties with >250,000 residents) between 1989 and 2000 (Woodruff et al., 2008, 098386). Only exposure during the first 2 mo of life was examined, and this was based on an average of CO concentrations recorded across all available monitors within the mother's county of residence. In contrast to the other postnatal mortality study in California, CO averaged over the first 2 mo of life was not associated with all-cause death (OR: 1.01 [95% CI: 0.94-1.09] per 0.5 ppm increase in 24-h CO concentration), or with respiratory related deaths (OR: 1.08 [95% CI: 0.91-1.54] per 0.5 ppm increase in 24-h CO concentration), SIDS (OR 0.85 [95% CI: 0.70-1.04] per 0.5 ppm increase in 24-h CO concentration), or other causes of postneonatal mortality (OR: 1.03 [95% CI: 0.96-1.09] per 0.5 ppm increase in 24-h CO concentration). These null findings may be due to higher error of the exposure assessment at the county level as opposed to using data from monitors within close proximity to the residence.

In a study that included 10 major cities in England, Hajat et al. (2007, 093276) created a daily time-series of air pollution and all infant deaths between 1990 and 2000. While there was no evidence for an association with neonatal deaths and ambient CO concentrations, there was a strong adverse effect of CO in postneonatal deaths, although the confidence intervals were wide due to a small sample size (RR 1.09, 95% CI: 0.94-1.25).

The only other postnatal mortality studies have been conducted throughout Asia. Two identical studies in Taiwan failed to find an association between daily counts of postneonatal deaths and ambient air pollutants, including CO. The data analyzed were from the cities of Taipei (Yang et al., 2006, 090760) and Kaohsiung (Tsai et al., 2006, 090709), with ambient CO concentrations being 1.6 ppm and 0.8 ppm, respectively. Both studies examined deaths for the period 1994-2000 and employed a case-crossover design that compared air pollution levels 1 wk before and after each infant's death.

Similarly, another study in South Korea examined postneonatal mortality for the period 1995-1999, using a time-series design. Same-day CO was not associated with all-cause death (RR: 1.02 [95% CI: 0.97-1.06] per 0.5 ppm increase). However, same-day CO was associated with postneonatal mortality when the analyses were restricted to respiratory mortality (RR: 1.33 [95% CI: 1.01-1.76] per 0.5 ppm increase) (Ha et al., 2003, 042552). An additional study examined the relationship between air pollution and postneonatal mortality for all causes in Seoul, Korea. This study used both case-crossover and time-series analyses for all firstborn infants during 1999-2003. The mean 8-h max CO concentration during this time period was 1.01 ppm. The association between ambient CO concentration and postneonatal mortality was the strongest in magnitude for CO when compared to the other criteria pollutants, though the confidence intervals were wide (RR: 1.02 [95% CI: 0.87-1.20] for case-crossover analysis; RR: 1.23 [1.06-1.44] for time-series analysis per 0.75 ppm increase in 8-h max CO concentration).

In general, the inconsistent exposure periods examined among these studies restricts direct comparison and interpretation. Nevertheless, there is limited evidence that CO is associated with an increased risk of infant mortality during the postneonatal period. The exposure periods examined varied from the same-day CO to lag periods up to a 6-mo period prior to birth, with one study alternatively exploring exposures averaged over the first 2 mo of life. Furthermore, given that birth weight and gestational age are strong predictors of infant mortality, in all of the reviewed studies these factors have not been considered at either the design or analysis stage. Hence, the link between fetal, neonatal, and postneonatal exposures, and the possible interaction that birth weight and

gestational age may have on the results yielded from these examined exposure periods needs further attention within this field of research.

5.4.1.5. Summary of Epidemiologic Studies of Birth Outcomes and Developmental Effects

There is some evidence that CO during early pregnancy (e.g., first month and first trimester) is associated with an increased risk of PTB. Additionally, there is evidence of ambient CO during pregnancy having a negative effect on fetal growth. In general, the reviewed studies (Figure 5-10 through Figure 5-12) reported small reductions in birth weight (~10-20 g). Although the majority of studies reported significant effects during either the first or third trimester, other studies failed to find a significant effect during these periods. Several studies examined various combinations of birth weight, LBW, and SGA/IUGR, and inconsistent results are reported across these metrics. For example, six studies reported an association between maternal exposure to CO and decreased birth weight, yet the decrease in birth weight did not translate to an increased risk of LBW or SGA. It should be noted that having a measurable, even if small, change in a population is different than having an effect on a subset of susceptible births, which may increase the risk of IUGR/LBW/SGA. It is difficult to conclude if CO is related to a small change in birth weight in all births across the population or a marked effect in some subset of births.

Three studies examined the effects of CO on cardiac birth defects and found maternal exposure to CO to be associated with an increased risk of cardiac birth defects. Human clinical studies also demonstrated the heart as a target for CO effects (Section 5.2). In general, there is limited evidence that CO is associated with an increased risk of infant mortality during the postneonatal period.

5.4.2. Toxicological Studies of Birth Outcomes and Developmental Effects

The brief overview of the reproductive and development toxicology of CO that follows is not limited to the past 10 yr as are other areas discussed in this document. This is because reproductive and developmental toxicology endpoints have not been covered in previous CO AQCDs. Effects of both exogenous CO exposure and endogenous production of CO are discussed since exposure to exogenous CO could possibly alter pathways normally regulated by endogenous CO production. This document details how in utero or perinatal CO exposure in pregnant dams or pups affects outcomes in the offspring, including postnatal mortality, skeletal development, the ability of the developing fetus to tolerate maternal dietary manipulation, behavioral outcomes, neurotransmitters, brain development, the auditory system, myocardial development, and immune system development. Similarly, endogenous CO is discussed in relation to pregnancy maintenance, vascular tone during gestation, the placenta, the ovaries, the anterior pituitary axis, and lactation. Together, this toxicological summary documents the importance of CO in reproductive and developmental toxicology in laboratory animal models.

5.4.2.1. Birth Outcomes

Decreased Birth Weight

Multiple reports have been published associating CO exposure in laboratory animals and decrements in birth weight (90-600 ppm); some of these studies also noted reduced growth evident in the prenatal period (65-500 ppm CO). Significant decreases in fetal body weight at GD21 after 21 days of continuous CO exposure (125, 250, or 500 ppm) in pregnant Wistar rats have been reported (Prigge and Hochrainer, 1977, 012326). This decrease was not found in rats exposed to 60 ppm CO. Penney et al. (1983, 011385) exposed pregnant rats to CO (200 ppm) for the final 17 days of prenatal development and also found significant decreases in near-term fetal rat weight at GD20-GD21; gestation in rats is ~ 22 days. Penney et al.(1982, 011387) continued to find decreased

body weight to PND210 after postnatal CO exposure (500 ppm, PND1-PND32) and to a larger extent in male pups when compared to female pups. Singh et al. (1984, 011409; 1993, 013892) found significant decreases in fetal weight in gestationally CO-exposed mouse pups (65, 125, 250 or 500 ppm) in two studies. Near-term fetal body weight was decreased at GD18 in mice exposed from GD7-GD18 to 125, 250, and 500 ppm CO but not 65 ppm CO (Singh and Scott, 1984, 011409). However, a second study found decreased fetal weight at GD18 with all CO exposures (65-500 ppm) from GD8-GD18 (Singh et al., 1993, 013892).

A number of studies have found decreases in birth weight after CO exposure. A decrease in body weight at birth was seen in neonates of pregnant rats exposed to 157, 166, and 200 ppm CO over GD6-GD19 (Penney et al., 1983, 011385). Singh (2006, 190512) showed decreases in birth weight of mouse pups gestationally exposed for 6 h/day for the first 2 wk of pregnancy to 125 ppm but not 65 ppm CO. Carmines and Rajendran (2008, 188440) exposed Sprague Dawley rats to ~600 ppm CO (dam COHb 30%) via nose-only inhalation (levels similar to those seen in cigarette smoke) during GD6-GD19 of gestation for 2 h/day and found significant decreases in birth weight (0.5 g or 13%) of exposed pups versus controls. Maternal body weight was unchanged through gestation, but corrected terminal body weight (body weight minus uterine weight) was significantly elevated in CO-exposed dams at term, indicating a decrease in uterine weight. Other studies have not found decreases in birth weight after gestational CO exposure (Carratu et al., 2000, 015839; Mereu et al., 2000, 193838).

Other animal models have been used to examine decreased birth weight resulting from CO exposure. Astrup et al. (1972, 011121) found significant decreases (11 and 20%, respectively) in birth weight of rabbits exposed to either 90 or 180 ppm CO continuously over the duration of gestation. Tolcos et al. (2000, 015997) found significant decreases in body, brain, and liver weights, and crown-to-rump length in guinea pig fetuses after exposure to 200 ppm CO for 10h/day from GD23-GD25 until GD61-GD63, at which time the fetuses were collected (term ranges from GD68 to GD72). In other studies, there was no significant differences in birth weight of guinea pig pups after a similar exposure (200 ppm from GD23-GD25 to term, fetal and maternal COHb levels of 13% and 8.5%, respectively) (McGregor et al., 1998, 085342; Tolcos et al., 2000, 010468) or in Long Evans rats (150 ppm CO continuous exposure over all of gestation) (Fechter and Annau, 1977, 010688). Fetal mouse weight was significantly greater than control in the 7 h/day exposures and significantly less than control animals in the 24 h/day (250 ppm CO, GD6-GD15) exposure groups, with corresponding significant differences in crown-to-rump length in the two groups (Schwetz et al., 1979, 011855). However, animals that showed no decrement in birth weight were significantly smaller at PND4 compared to control guinea pigs (McGregor et al., 1998, 085342), with dam and fetal COHb levels of 13% and 8.5%, respectively, during pregnancy.

Pregnancy Loss and Perinatal Death

Two studies have provided evidence for CO-induced pregnancy loss and perinatal death at CO concentrations between 90 and 250 ppm. Schwetz et al. (1979, 011855) exposed CF-1 mice and New Zealand rabbits to 250 ppm CO over GD6-GD15 (mice) or GD6-GD18 (rabbits) for either 7 h/day or 24 h/day, yielding 4 exposure paradigms. The fetuses were then collected at the termination of exposure, near term. Maternal COHb in the 7 h/day exposure groups was approximately 10-15% COHb in rabbits and mice; COHb was not followed in the 24-h exposure groups. The mice exposed to CO for 7 h/day but not 24 h/day had a significant increase in the number of resorbed pups. Rabbits were less affected by CO exposure, manifesting no significant perinatal death or pregnancy loss. Astrup et al. (1972, 011121) studied the effect of CO on fetal development after continuous CO exposure (90 or 180 ppm CO, COHb 8-9% and 16-18%, respectively) over the duration of gestation in rabbits. In the immediate neonatal period, 24 h postpartum, 35% (180 ppm) and 9.9% (90 ppm) of CO-exposed animals died. In the postpartum period after the first 24 h and extending out to PND21, 90 ppm CO-exposed pups experienced 25% mortality versus 13% in controls; there was no difference from control at the 80 ppm CO exposure level. Gestation length was unchanged with CO exposure. Conversely, Fechter and Annau (1977, 010688) exposed Long Evans rats in utero to 150 ppm CO continuously through gestation (dam COHb 15%) and saw no effects of CO on litter mortality at PND1.

Effect of Maternal Diet

As mentioned above, CO induced offspring mortality after prenatal exposure. Alterations in maternal dietary protein and zinc further altered offspring mortality and teratogenicity caused by CO (65-500 ppm).

Maternal Protein Intake and Neonatal Mouse Mortality and Teratogenicity

Pregnant CD-1 mice were exposed intermittently (6 h/day for first 2 wk of pregnancy) to CO (0, 65, or 125 ppm) in combination with protein modified diets (27% [supplemental protein], 16% [control], 8% [low], or 4% [very low protein]) to assess the role of dietary protein in modulating CO effects on neonatal mortality at 1 wk of age (Singh, 2006, 190512). Litter size was not affected by CO exposure. Pup weight was inversely related to CO exposure and directly related to dam diet protein content during pregnancy. Pup mortality at birth was directly related to CO exposure in certain protein groups (supplemental, and 4% protein) and inversely related to the dam's dietary protein content. At 1 wk of age, pup mortality was significantly increased by CO exposure as well as dietary protein restriction; all pups in the 4% protein diet died by 1 wk of age. CO exposure (65 ppm only) combined with a normal protein diet (16%) and CO exposure (65 and 125 ppm) with a supplemental protein diet (27%) significantly increased pup mortality at 1 wk versus control air pups (0 ppm CO). Contrary to other findings, low protein diet (8%) combined with CO (125 ppm) led to a slight yet significant decrease in pup mortality at 1 wk of age versus control (0 ppm CO). In summary, these data show that in utero CO exposure induced increased neonatal mouse deaths at 1 wk in supplemental protein and normal protein diet exposure groups and increased perinatal mortality when combined with supplemental or restricted protein.

The role of diet as a contributor to teratogenicity of CO (0, 65, 125, or 250 ppm CO) in CD-1 mice given various protein diets (4, 8, 16, or 27% protein) during pregnancy was explored by Singh et al. (1993, 013892). Timed-pregnant CD-1 mice were exposed continuously to CO from GD8-GD18, at which point animals were sacrificed and fetuses collected. Work by this group has shown that low protein diets plus CO exposure act in an additive fashion to increase placental COHb in mice (Singh, 2003, 053624; Singh et al., 1992, 013759). As expected, all levels of CO and the lowest protein diet (4 or 8% protein) given to the dams during gestation resulted in significantly decreased near-term weight of normal fetuses at GD18. CO exposure did not produce maternal toxicity except for a significant decrease in maternal weight at GD18 with 4 and 8% protein diets versus control diet in non-CO-exposed animals. Dam dietary protein levels were inversely related to gross fetal malformations including jaw changes. All concentrations of CO exposure within each maternal dietary protein level significantly increased the percentage of litters with malformations in a dose-dependent manner. Skeletal malformations were present in offspring, with the percent of litters affected inversely related to dietary protein levels. CO exposure concomitant with a low protein diet increased the percent of skeletal malformations in offspring. The percent of dead, resorbed, or grossly malformed fetuses was directly related to CO concentration and inversely related to maternal dietary protein levels. CO and maternal dietary protein restriction had a synergistic effect on mouse offspring mortality and an additive effect on malformations.

Maternal Zinc and Protein Intake and Neonatal Mortality and Teratogenicity

Singh (2003, 053624) explored how teratogenicity and fetal mortality were affected by zinc (Zn) modulation in CO-exposed (500 ppm from GD8-GD18) pregnant dams (CD-1 mouse) given protein-insufficient diets. CO exposure in low-protein conditions (9% protein) decreased the mean implants per litter as compared to air exposure. CO exposure also increased the near-term fetal mortality over all groups, and to a larger extent in the low-protein groups, both Zn normal (57% versus 6% mortality) and Zn deficient groups (86.6% versus 70.9% mortality). Under low-protein conditions, CO exposure increased the incidence of malformations (9.4% versus 0%) when Zn levels were normal and increased the incidence of gastroschisis (5% versus 0%) when Zn levels were low. Joint protein and Zn deficiency led to 60% of litters with gastroschisis. Conversely, CO exposure under Zn deficiency decreased the incidence of other malformations such as exencephaly, jaw, syndactyly, and tail malformations.

Further studies by Neggers and Singh (2006, 193964) only partially confirmed these findings. As before, diets deficient in both Zn and protein had significant detrimental influence on both fetal malformations and mortality. Exposure to 500 ppm CO increased fetal mortality and malformation

rates under deficient protein (9%) and supplemental Zn (3.3 g/kg diet) conditions; however, CO had a negligible effect on these endpoints under deficient protein and deficient or normal Zn conditions.

Role of Endogenous CO

CO is produced endogenously from heme protein catabolism by heme oxygenases, HO-1, HO-2, and HO-3. CO has recently been recognized as a second messenger signaling molecule, similar to NO, with a number of normal physiological roles in the body. Some of these roles are played in maintaining pregnancy, controlling vascular tone, regulating hormone balance, and sustaining normal ovarian follicular maturation. These areas could be potential areas of interaction of exogenous CO.

Pregnancy Maintenance

HO-1 is known to protect organs from rejection (Kotsch et al., 2006, 193899) and thus, HO may also protect the developing fetus from rejection by the non-self maternal immune system. Idiopathic spontaneous abortions are more frequent in women with HO-1 polymorphisms (GT)n microsatellite polymorphisms associated with altered HO-1 transcription in their genome (Denschlag et al., 2004, 193894). Similarly, administering HO-inhibitors to pregnant rodents induced total litter loss, possibly due to vasoconstriction and associated ischemia of the placental vascular bed (Alexandreanu and Lawson, 2002, 192373). Also, mice overexpressing HO-1 had a significantly decreased rate of spontaneous abortion (Zenclussen et al., 2006, 193873). Various pathologies of pregnancy, including IUGR and pre-eclampsia, are associated with significant decreases in placental HO activity (Denschlag et al., 2004, 193894; McLaughlin et al., 2003, 193827). Oxygenation is important in early pregnancy and triggers trophoblast invasion of the spiral arteries (Kingdom and Kaufmann, 1997, 193897). Women living at high altitude have an increased risk of adverse pregnancy outcomes versus women living at lower altitudes (Zamudio et al., 1995, 193908). Also, women living at high altitude, women with pre-eclampsia, or women who had pregnancies with fetal growth restrictions (FGR) produced term placenta with significant decreases in HO-2 versus women living at lower altitude with uncomplicated pregnancies (Barber et al., 2001, 193891; Lyall et al., 2000, 193902). Thus, the HO/CO system is crucial for the developing fetus, helps in maintaining pregnancy, and plays a role in spontaneous abortions.

Vascular Control

During pregnancy, there is increased blood volume without a concurrent increase in systemic BP, which is accomplished by a decrease in total peripheral vascular resistance (Zhao et al., 2008, 193883). CO through the production of soluble guanylate cyclase is able to stimulate the relaxation of vascular smooth muscle (Villamor et al., 2000, 015838) and relaxation of pregnant rat tail artery and aortic rings (Longo et al., 1999, 011548). Further, the administration of the HO inhibitor SnMP increased maternal BP (systolic, diastolic, and mean arterial pressure) and significantly increased uterine artery blood flow velocity during pregnancy in mice (Zhao et al., 2008, 193883). Zhao et al. also showed pregnancy induced increased total body CO exhalation and that this increased CO production could be significantly decreased by SnMP administration. Abdominal aortas (AA) of pregnant dams are significantly dilated with pregnancy, and SnMP treatment leads to AA vasoconstriction to levels similar to nonpregnant mice. Isolated human placenta exposed to solutions containing CO demonstrated a concentration-dependent decrease in perfusion pressure (Bainbridge et al., 2002, 043161), further demonstrating the role of CO in maintaining basal vasculature tone. However, the addition of exogenous CO to isolated human and rat uterine tissue during pregnancy failed to induce relaxation and quiet the spontaneous contractility of rat or human myometrium (uterine smooth muscle)(Longo et al., 1999, 011548). CO is not able to relax all types of vascular smooth muscle (Brian et al., 1994, 076283), and pregnancy appears to modulate the response of tissues to CO (Katoue et al., 2005, 193896). Thus, it appears that the increased CO production during pregnancy may partially account for the decreased peripheral vascular resistance seen in pregnancy that prevents the increased blood volume of pregnancy from affecting BP.

Hormone Regulation

Endogenous CO has been shown to regulate neuroendocrine functions. Disruption of normal CO signaling causes changes in the cycles of a number of hormones involved in pregnancy. HO inhibition in rats significantly decreased ovarian production of gonadotrophin-induced androstenedione and progesterone without affecting estradiol levels (Alexandreanu and Lawson, 2002, 192373). However, treatment with the HO-inducer, hemin, caused androstenedione and estradiol production from rat ovaries in vitro. CO also has been shown to have a stimulatory effect on gonadotropin-releasing hormone (GnRH) release from rat hypothalamic explants in vitro (Lamar et al., 1996, 078819), while in vivo CO appears not to influence GnRH secretion (Kohsaka et al., 1999, 191000). HO-1 induction and HO concentration have been shown to be regulated by estrogen in the rat uterus (Cella et al., 2006, 193240) during pregnancy and in nongravid rats. This agrees with work by Tschugguel et al. (2001, 193785) in which CO was generated by primary endothelial cells from human umbilical veins and uterine arteries after exogenous 17-β estradiol administration. HO inhibition by CrMP decreased time in estrous in a dose-dependent manner (Alexandreanu and Lawson, 2002, 192373).

HO-1 and HO-2 are expressed in rat anterior pituitary, and the secretion of gonadotropins and prolactin is affected by HO-inhibitor and HO-substrate administration (Alexandreanu and Lawson, 2003, 193871). The estrogen-induced afternoon surge of luteinizing hormone (LH) was advanced forward in time by HO inhibition, and this advance could be reversed by concomitant administration of hemin. The serum follicle stimulating hormone (FSH) surge was unaffected by HO inhibition or hemin, but in vitro treatment of GnRH-stimulated pituitaries with hemin led to a significant increase in FSH release. The estrogen-dependent afternoon prolactin surge was inhibited or delayed by HO inhibition and significantly decreased prolactin release. In vitro studies using pituitary explants showed that LH release was significantly increased by HO inhibition. HO inhibition also decreased litter weight gain during lactation, which the authors attributed to decreased maternal milk production or milk ejection problems as cross-fostered pups regained weight that was lost during nursing on HO-inhibited dams (Alexandreanu and Lawson, 2002, 192373). The lactational effects seen in this model may be explained by changes in prolactin (Alexandreanu and Lawson, 2003, 193871). It is possible that HO inhibition by CrMP may also inhibit NO production, a mechanism that is distinct from CO-dependent effects.

Ovarian Follicular Atresia

As a part of normal follicular maturation in the ovaries, the majority of follicles undergo atresia via apoptosis prior to ovulation. Harada et al. (2004, 193920) harvested porcine granulosa cells from ovaries and found that cells naturally undergoing atresia or cell death more strongly expressed HO-1 than did successful follicles. Addition of the HO-substrate hemin or the HO-inhibitor Zn protoporphyrin IX (ZnPP IX) significantly induced or inhibited granulosa cell apoptosis, respectively. In this porcine model, HO was able to augment granulosa cell apoptosis allowing for proper follicular maturation.

Summary of Toxicological Studies on Birth Outcomes

There is some evidence that CO exposure leads to altered birth outcomes, including decreased birth and near-term body weight, increased pregnancy loss and perinatal death, and increased malformations. These events occurred at levels as low as 65 ppm for fetal body weight decrements and 90 ppm for changes in birth weight and perinatal death. Pregnancy loss was seen after exposure to 250 ppm CO, whereas skeletal malformations were present after 180 ppm CO. Dietary protein and zinc modifications exacerbated these CO-induced effects on birth outcomes. Maternal protein restriction and CO had a synergistic effect on peri- and postnatal mortality and an additive effect on malformations. Dietary zinc alterations resulted in inconsistent changes to CO-induced malformations and fetal mortality.

Endogenous CO is recognized as a second messenger signaling molecule with normal physiological roles in maintaining pregnancy and for proper fetal and postnatal development. The endogenous HO/CO system is also involved in controlling vascular tone, follicular maturation, ovarian steroidogenesis, secretion of gonadotropin and prolactin by the anterior pituitary, lactation,

and estrous cyclicity in rodent studies. These areas could be potential points of interaction of exogenous CO with endogenous HO/CO.

5.4.2.2. Developmental Effects

Congenital Abnormalities

Studies by Schwetz et al. (1979, 011855) found that gestational CO exposure (250 ppm) in CF-1 mice for 7 or 24 h/day over GD6-GD15 resulted in minor fetal skeletal alterations in the form of extra lumbar ribs and spurs (dam gestational COHb 10-15% for 7h/day exposure, 24 h/day dam COHb not measured). Similarly exposed rabbits did not exhibit these changes.

Astrup et al. (1972, 011121) studied the effect of CO exposure on fetal rabbit development via continuous CO exposure (90 or 180 ppm with gestational dam COHb of 9 and 17%, respectively) over the duration of gestation. Three pups in the 180 ppm CO group (n = 123) had deformities in their extremities at birth, whereas no control and no 90 ppm CO-exposed animals manifested with this malformation.

Further skeletal malformations were seen after gestational CO exposure in mice as described above ("Effect of Maternal Diet") (Singh et al., 1993, 013892). Briefly, pregnant CD-1 mice were exposed intermittently to CO (65-250 ppm; GD8-GD18) in combination with protein modified diets (27% [supplemental protein], 16% [control], 8% [low], or 4% [very low protein]) to assess the role of dietary protein in modulating CO effects on neonates at 1 wk of age. Maternal dietary protein restriction additively compounded the CO-induced skeletal malformations. Further, dietary restriction in Zn and protein led to increased teratogenicity, specifically increased incidence of gastroschisis (Singh, 2003, 053624). Conversely, Carmines and Rajendran (2008, 188440) did not find evidence of external malformations (teratogenicity) in rats after exposure to ~600 ppm CO from GD6-GD19.

CNS Developmental Effects

Behavioral

Investigators have used animal models to study the effects of moderate CO exposure (65-150 ppm) during gestation on behavioral outcomes after birth, including active avoidance, learning and memory, homing, and motor activity. These studies generally found decrements in behavior in early life after in utero exposure to CO concentrations >125 ppm and in some cases as low as 65 ppm. Table 5-14 shows results of behavioral response studies with CO exposure $\leq$ 150 ppm.

Table 5-14. Behavioral responses.

Study	Model System	CO Exposure	Response	Notes
BEHAVIORAL RESPONSES				
De Salvia et al. (1995, 079441)	Rats	75 and 150 ppm continuous GD0-GD20	Impaired acquisition (3 and 18 mo) and reacquisition (18 mo) of avoidance behavior at 150 ppm, not 75 ppm	
Mactutus and Fechter (1985, 011536)	Rats	150 ppm continuous GD0-GD20	Delayed acquisition of active avoidance (PND120) and disrupted retention (PND360)	COHb 15.6 ± 1.1%
Di Giovanni et al. (1993, 013822)	Rats	75 and 150 ppm continuous GD0-GD20	CO (150 ppm) reduced the minimum frequency of ultrasonic calls as well as decreased responsiveness to a challenge dose of diazepam. There was no change in locomotion; however, CO impaired learning in a two-way active avoidance task.	
Mactutus and Fechter (1984, 011355)	Rats	150 ppm	Acquisition did not improve with age/maturation, failure to learn; impaired reacquisition (PND31), failure to retain	COHb 15%
Giustino et al. (1999, 011538)	Rats	75 and 150 ppm continuous GD0-GD20	Decreased exploration, habituation, nonspatial working memory	COHb: 1.6 ± 0.1% (0 ppm); 7.36 ± 0.2% (75 ppm); 16.1 ± 0.9% (150 ppm)
Zhuo et al. (1993, 013905)	Mouse hippocampal brain sections	ZnPPIX (HO inhibitor) and 0.1-1.0 µM CO	HO inhibition blocked long-term potentiation and CO evoked synaptic potentials and long-term enhancement	
Stevens and Wang (1993, 188458)	Mouse and rat hippocampal brain slices	ZnPPIX (5-15 µM)	HO inhibition blocked long-term potentiation but not long-term depression.	
Mereu (2000, 193838)	Rat hippocampal brain sections	150 ppm GD0-GD20	Impaired long-term potentiation maintenance	
Fechter and Annau (1980, 011295)	Rats	150 ppm continuous GD0-GD20	Delayed homing behavior and poor reflexive response	
Fechter and Annau (1977, 010688)	Rats	150 ppm continuous GD0-GD20	Decreased locomotor activity at PND1, PND4, and PND14, but not PND21	COHb 15%
Singh (1986, 012827)	Mice	65 and 125 ppm continuous GD7-GD18	Impaired aerial righting score at PND14 (65 and 125 ppm), impaired negative geotaxis at PND10 and righting reflex on PND1 (125 ppm)	

Active Avoidance Behavior. To assess behavioral changes after in utero exposure, pregnant Wistar rats were exposed to CO (0, 75, or 150 ppm) continuously over GD0-GD20 (De Salvia et al., 1995, 079441). Male pups from exposed dams were evaluated for active avoidance behavior (mild shock avoidance) during acquisition and reacquisition. This work was designed to expand on the studies of Mactutus and Fechter (1985, 011536), who showed delayed acquisition (120 days of age) of an active avoidance task and disruption of retention at a later test date (360 days) after continuous in utero CO exposure (150 ppm CO, dam COHb concentrations of 15.6 ± 1.1%), and to determine if these behavioral changes were permanent. De Salvia et al. (1995, 079441) found there were no significant behavioral impairments following exposure to 75 ppm CO. However, animals exposed to the 150 ppm in utero had significantly impaired acquisition (at 3 and 18 mo of age) and reacquisition (at 18 mo of age) of conditioned avoidance behavior. This impaired learning was also seen in gestationally CO (150 ppm, trend seen at 75 ppm) exposed rats at PND90 (Di Giovanni et al., 1993, 013822). The authors speculated that this CO-dependent behavioral change may be mediated through neurotransmitter signaling, specifically changes in dopamine in the neostriatum or nucleus accumbens. These studies demonstrate that moderate CO exposure in utero can lead to permanent behavioral changes in male offspring.

Mactutus and Fechter (1984, 011355) also found that acquisition in a two-way conditioned avoidance test (flashing light warnings followed by mild footshock) failed to improve with age of in

utero CO-exposed (150 ppm, dam COHb 15%) Long Evans rats (male and female offspring) in contrast to air-exposed controls who improved with age/maturation, indicating a failure in the associative process of learning. They also found impairments in reacquisition performance, an index of retention, in PND31 rats that had received continuous in utero CO exposure. Overall, prenatal CO exposure (150 ppm, not 75 ppm) induced learning and memory deficits in male and female offspring.

Habituation, Memory, and Learning. Giustino et al. (1999, 011538) exposed primiparious pregnant Wistar rats to CO (0, 75 or 150 ppm) by inhalation from GD0-GD20. Blood COHb concentrations (mean % ± SEM) on GD20 were reported (0 ppm: 1.6 ± 0.1; CO 75 ppm: 7.36 ± 0.2; CO 150 ppm: 16.1 ± 0.9). Male offspring at age 40 days were given two habituation trials. In the first trial (T1), two similar objects were presented. In the second trial (T2), one object from the first trial was presented as well as one novel object. Results were quantified three ways. Exploration activity was defined as the time exploring both objects during each trial. Global habituation was quantified as a comparison of the time spent exploring the two objects in T1 to the time spent exploring objects in T2. Discrimination between new and familiar objects was measured in T2 by contrasting the time spent exploring the familiar object to the time spent exploring the new object. These recognition sessions test for the preference that rats have for investigating novel objects in lieu of familiar objects and are a measurement of nonspatial working memory. The results of this study showed 40 day old animals that were gestationally exposed to CO (both 75 and 150 ppm) spent less time exploring novel objects when compared to control animals. Control rabbits habituated or learned after a second exposure to a previously explored object (T2<T1), but T2 and T1 were not significantly different with CO exposure (150 ppm). Results for rats exposed to 75 ppm were inconsistent in that significantly different exploratory times were found using one statistical method (Wilcoxon paired signed-rank test) and not found using another method (Kruskal-Wallis ANOVA). Finally, the decreased time spent with a familiar object by control rats was not seen in CO-exposed animals (75 or 150 ppm). The authors speculated that the mesolimbic dopaminergic system may be responsible for these changes, possibly involving the nucleus accumbens. The human literature shows a possible connection with these CO-dependent rodent effects; infants whose mothers smoked during pregnancy manifest with habituation defects (Fried et al., 1998, 190210; Fried et al., 2003, 190209). Nonetheless, CO is just one of many constituents of cigarette smoke. The results from these animal toxicology studies showed that in utero exposure to CO affects nonspatial working memory in young adult male rats.

Studies have shown that endogenous and exogenous CO may be involved in the generation of the hippocampal long-term potentiation (LTP), which is believed to correlate with learning and memory (Hawkins et al., 1994, 076503; Mereu et al., 2000, 193838; Stevens and Wang, 1993, 188458; Zhuo et al., 1993, 013905). It is possible that CO can act as a retrograde synaptic signaling messenger, allowing a signal to travel from a postsynaptic to presynaptic neuron. Treatment of mouse or rat hippocampal brain sections with ZnPPIX, an HO-inhibitor, blocked induction of the LTP but not long-term depression (Stevens and Wang, 1993, 188458; Zhuo et al., 1993, 013905). Exogenous CO exposure (0.1-1.0 µM) also evoked long-term enhancement and evoked synaptic potentials (Zhuo et al., 1993, 013905). Similarly, hippocampal slices from gestationally CO-exposed (150 ppm from GD0-20) Wistar rats exhibited an impaired ability to maintain LTP over time and a modest reduction in post-tetanic potentiation (Mereu et al., 2000, 193838). Conversely, other studies have found no correlation between CO and LTP using step-through, step-down, and water-maze tests (Bing et al., 1995, 079418; Toyoda et al., 1996, 079945). Thus, distinct types of learning may be differentially regulated by CO exposure, and endogenous CO, as modulated by HO-inhibitors, may manifest with different outcomes when compared to outcomes seen for exogenous CO.

Homing and Locomotor Effects. Fechter and Annau (1977, 010688; 1980, 011295) exposed Long Evans rats in utero to 150 ppm CO continuously through gestation (dam COHb 15%) and saw significant effects of CO on pup locomotor activity measured across 10-min intervals for a 1-h period. CO-exposed pups showed consistently less activity than air-exposed controls through the preweaning window, with significantly reduced activity seen at PND1 and PND4 (both after subcutaneous L-DOPA administration to induce movement) and at PND14 but not at PND21. However, the PND14 rats only showed decreased activity after 30 min of testing. Di Giovanni et al. (1993, 013822) found that prenatal CO (75 and 150 ppm) did not significantly affect locomotor activity or D-amphetamine induced hyperactivity at PND14 or PND21, but the rats were only subjected to a 30-min session. This study may have overlooked the later window of possible decreased activity.

Under analogous exposure conditions, Fechter and Annau (1980, 011295) found that the development of homing behavior, orientation by the rat toward its home cage, was significantly delayed in rats prenatally exposed to 150 ppm CO. Also, exposed offspring manifested with poorer than normal performance on the negative geotaxis test, a reflexive response that results in a directional movement with or against gravity. Similarly, continuous prenatal CO exposure (125 ppm, GD7-GD18) in CD-1 mice impaired negative geotaxis at PND10 (Singh, 1986, 012827). The standardization and use of geotaxis as a vestibular, motor, or postural metric in infant rodents has been debated in the literature (Kreider and Blumberg, 2005, 193944).

Prenatal exposure to CO (125 ppm, GD7-GD18) significantly affected the righting reflex (the turning of an animal from its supine position to its feet) in exposed CD-1 mice on PND1. Also, the aerial righting score, or turning 180° and landing on the feet when dropped from the supine position at a height, was significantly decreased in pups exposed to CO in utero (65 and 125 ppm) at PND14 (Singh, 1986, 012827). The same trend of impaired righting reflex was seen in gestationally CO (150 ppm) exposed rats (Fechter and Annau, 1980, 011295). These behavioral tests indicated neuromuscular, vestibular, or postural effects in the CO-exposed neonate.

Conversely, no gross impairment of motor activity was found as measured by infrared movement monitoring in Wistar rats treated in utero (GD0-GD20) with 0, 75 or 100 ppm CO (Carratu et al., 2000, 015839). Monitoring was done at PND40 and PND90 and may have been too late to detect CO-dependent changes. Earlier studies by Fechter and Annau (1977, 010688) identified an early window of sensitivity for CO-dependent motor activity deficits of PND1-PND14, with recovery by PND21.

Emotionality. In utero CO exposure caused subtle alterations in the ontogeny of emotionality measured by the ultrasonic vocalization emitted by rat pups removed from their nest. Prenatal CO exposure (150 ppm) caused a reduction in the minimum frequency of ultrasonic calls emitted by PND5 pups (Di Giovanni et al., 1993, 013822). The rate of calling, maximum frequency, and duration and sound pressure level were not affected by prenatal CO. However, the rate of calling and responsiveness to a challenge dose of diazepam was decreased by prenatal CO exposure. Pup vocalization is mediated by the GABAergic neuron function which is altered by CO exposure (see below).

Neuronal

Since behavioral changes have been caused by CO exposure, studies have investigated whether CO exposure results in changes to neuronal structures and electrical excitability. Moderate levels of CO (75 -150 ppm) decrease peripheral nervous system (PNS) myelination due to impaired sphingomyelin homeostasis and can reversibly delay the rate of ion channel development after gestational exposure. In utero CO exposure also results in irreversible changes in sodium equilibrium potential. Further details of these studies are given below in Table 5-15.

Table 5-15. Neuronal responses.

Study	Model System	CO Exposure	Response	Notes
NEURONAL RESPONSES				
Carratu et al. (2000, 015839)	Rats	75 and 150 ppm continuous GD0-GD20	Decreased peripheral nerve fiber myelin sheath thickness	COHb: 0 ppm (GD10: 0.97 ± 0.02; GD20: 1.62 ± 0.1.), 75 ppm (GD10: 7.20 ± 0.12; GD20: 7.43 ± 0.62), and 150 ppm (GD10: 14.42 ± 0.52; GD20: 16.08 ± 0.88)
Carratu et al. (2000, 015935)	Rats	150 ppm continuous GD0-GD20	Impaired sphingomyelin homeostasis by increasing sphingosine	
Carratu et al. (1993, 013812)	Rats	75 and 150 ppm continuous GD0-GD20	Produced partly reversible changes in membrane excitability through delayed inward current inactivation and decreased inward current reversal potential	COHb: 15% at 150 ppm
De Luca et al. (1996, 080911)	Rats	75 and 150 ppm continuous GD0-GD20	Delayed development of the ion channels responsible for passive and active membrane electrical properties of skeletal muscle	
Montagnani et al. (1996, 080902)	Rats	75 or 150 ppm GD0-GD20	CO (150 ppm) increased the tetrodotoxin-inhibition of PNS-evoked vasoconstriction at PND5-7. CO exposure caused the relaxant effect by ACh to appear earlier and the contractile response to disappear earlier (vasodilator effects).	
Dyer et al. (1979, 190994)	Rats	150 ppm GD0-GD21	Increased early components (P1-N1 and N1-P1) of the cortical flash evoked potential peak-to-peak amplitudes at PND65 in female rats	Maternal COHb: 15%

Peripheral Nerve Myelination. The effect of in utero exposure (GD0-GD20) to 0, 75 or 150 ppm CO on sciatic nerve myelination in male offspring was studied in Wistar rats (Carratu et al., 2000, 015839). The dam CO blood concentration, expressed as % COHb, was determined for 0 ppm (GD10: 0.97 ± 0.02; GD20: 1.62 ± 0.1.), 75 ppm (GD10: 7.20 ± 0.12; GD20: 7.43 ± 0.62), and 150 ppm (GD10: 14.42 ± 0.52; GD20: 16.08 ± 0.88). The myelin sheath thickness of the peripheral nerve fibers was significantly decreased in CO-exposed animals (75 and 150 ppm); however, axon diameter was not affected. As mentioned above, even though CO affected myelination, it did not significantly affect motor activity of CO-exposed mice at 40 and 90 days. It is possible that these deficits in PNS myelination are due to impaired sphingomyelin homeostasis. In utero exposure (GD0-GD20) of Wistar rats to CO (150 ppm) caused a twofold increase in sphingosine (SO) but not sphinganine (SA) in the sciatic nerve at 90 days of age (Carratu et al., 2000, 015935). SO is an intermediate in sphingolipid turnover and SA is an intermediate of de novo sphingolipid biosynthesis. Hypoxia has been shown to induce sphingomyelin changes which could lead to impaired myelination and motor activity decrements (Ueda et al., 1998, 195136; Yoshimura et al., 1999, 195135). Prenatal CO exposure had no effect on brain SA or SO levels in male offspring at 90 days of age. These results demonstrate prenatal CO exposure could interrupt sphingolipid homeostasis in the PNS but not CNS, causing a decrease in nerve myelination without changes in motor activity.

Electrophysiological Changes.

Gestational exposure of Wistar rats to continuous CO (75 or 150 ppm (15% COHb at 150 ppm) yielded electrophysiological changes in the PNS (Carratu et al., 1993, 013812). Changes were noticeable in voltage- and time-dependent properties of sodium channels in the sciatic nerve after in utero CO exposure. Changes in sodium channel inactivation kinetics were reversible (present at PND40 and absent at PND270) but changes in the sodium equilibrium potential were irreversible. In utero CO exposure (150 ppm) also delayed the development of the resting chloride conductance (GCl) and resting potassium conductance (GK), with levels matching the control by PND80 and PND60, respectively (De Luca et al., 1996, 080911). CO exposure (75 and 150 ppm) also altered the pharmacological properties of the chloride channel and excitability parameters of skeletal muscle fibers. These changes in the nerve electrophysiological properties could account for increased

tetrodotoxin-inhibition of the vasoconstriction evoked by the PNS in 5- to 7-day-old prenatally exposed pups (Montagnani et al., 1996, 080902). Finally, gestational CO exposure increased early components (P1-N1 and N1-P1) of the cortical flash evoked potential peak-to-peak amplitudes at 65 days postexposure (PND65) in female, not male, rats (Dyer et al., 1979, 190994). The early waves of the cortical evoked potential, an indicator of visual cortical functioning, generally indicate activity in the retinogeniculostriate system. These studies showed that in utero CO exposure had both reversible and irreversible effects on sodium and potassium channels, which are essential for proper electrophysiological function of the muscles and PNS.

Neurotransmitter Changes

The developing nervous system is extremely sensitive to decreased oxygen availability. Virtually all neurotransmitter systems are present at birth but require further maturation. The studies listed below in Table 5-16 have shown that prenatal exposure to CO alters a number of neurotransmitters and their pathways at concentrations ranging from 75 to 300 ppm, both transiently and permanently.

Medullar Neurotransmitters. SIDS is a complex syndrome that involves the aberrant development of brain stem nuclei controlling respiratory, cardiovascular, and arousal activity. To investigate changes in the structure and neurochemistry of the brain stem, Tolcos et al. (2000, 015997) exposed pregnant guinea pigs to CO (200 ppm) over the last 60% of gestation. Guinea pigs and humans both have the majority of CNS development in utero. CO-exposed pups were found to have significant decrements in body, brain, and liver weights, crown-to-rump length, and medullar volume when compared to control pups. Neurotransmitter systems were also affected after CO exposure. Specifically, the brain stem displayed significant decreases in protein and immunoreactivity for tyrosine hydroxylase (TH), an enzyme necessary for catecholamine production, which is likely due to decreased cell number in specific medullar regions responsible for cardiorespiratory control. This was consistent with earlier work showing that prenatal CO exposure leads to aberrant respiratory responses to asphyxia and CO_2 (McGregor et al., 1998, 085342). The cholinergic system was also affected by prenatal CO exposure with significant increases in choline acetyl-transferase (ChAT) immunoreactivity of the medulla; however, no changes in muscarinic acetylcholine receptor were seen. This is in contrast to human infants with SIDS who show decreased brain stem muscarinic receptor binding (Kinney et al., 1995, 193898). ChAT changes in this study (Tolcos et al., 2000, 015997) were from areas of the medulla associated with tongue innervation, which is crucial to swallowing, possibly in relation to breathing.

A second risk factor for SIDS is hyperthermia. To explore the interaction of hyperthermia and CO-induced hypoxia, pregnant guinea pigs were exposed to CO (0 or 200 ppm) for 10 h/day for the last 60% of gestation (Tolcos et al., 2000, 010468). At PND4 male pups were exposed to hyperthermia or ambient temperature as a control. Brains were then collected at 1 and 8 wk of age. In utero CO exposure sensitized some areas of the brain to future hyperthermic insults. Specifically, CO plus hyperthermia induced significant increases in serotonin in multiple brain regions (NTS, DMV, and hypoglossal nucleus) at 1 wk of age; this change was no longer evident at 8 wk of age. Hyperthermia exposure alone induced decreased met-enkephalin neurotransmitter immunoreactivity at 1 wk of age that was absent at 8 wk and absent in CO-plus-hyperthermia exposed animals. Brain stem neurotransmitter (met-enkephalin, serotonin, TH, substance P) immunohistochemical differences were not apparent with CO treatment alone. At 8 wk of age, CO-plus-hyperthermia exposure induced glial aggregations and gliosis surrounding infarct or necrotic areas in the brain and the medulla lesions stained positive for glial fibrillary acidic protein (GFAP). GFAP upregulation is classically seen with neuronal diseases or following neurodegeneration. Gross structural observations revealed no differences in the medulla or cerebellum following in utero CO exposure alone. Together, these data showed that CO exposure in utero sensitizes the brain to future hyperthermic insults, lea ding to generation of necrotic lesions in the brain and changes in neurotransmitter levels.

Table 5-16. Neurotransmitter changes.

Study	Model System	CO Exposure	Response	Notes
NEUROTRANSMITTER CHANGES				
Tolcos et al. (2000, 015997)	Guinea pigs	200 ppm 10h/day GD23-GD25 to GD61-GD63	CO affected catecholaminergic system in brain stem by reducing tyrosine hydroxylase. Affected cholinergic system by increasing choline acetyl-transferase.	Fetal COHb: 13% Maternal COHb: 8.5%
Tolcos et al. (2000, 010468)	Guinea pigs	200 ppm 10h/day GD23-GD25 to birth Hyperthermia on PND4	CO sensitizes the brain to the effects of a short period of hyperthermia on PND4. The exposure combination resulted in lesions in the brain, as well as increased serotonin and glial fibrillary acidic protein. The exposure also caused reactive astrogliosis.	Fetal COHb: 13% Maternal COHb: 8.5%
McGregor et al. (1998, 085342)	Guinea pigs	200 ppm 10h/day GD23-GD25 to birth	CO increased tidal volume during steady state hypercapnia and progressive asphyxia, due to increased ventilation.	Fetal COHb: 13% Maternal COHb: 8.5%
Cagiano et al. (1998, 087170)	Rats	75 and 150 ppm GD0-GD20	In utero CO (150 ppm) exposure increased mount/intromission latency , decreased mount/intromission frequency, and induced ejaculatory abnormalities. CO also blunted the amphetamine-induced increase in dopamine.	Maternal COHb: GD10: 1, 7, and 15%; GD20: 1.5, 7, and 16% (0, 75, and 150 ppm CO, respectively)
Hermans et al. (1993, 190510)	Rats	Hypoxia (10.5% O_2) GD15-GD21	Hypoxia caused delayed initiation latencies of male sexual behavior and decreased number of ejaculations.	
Fechter et al. (1987, 012259)	Rats	75, 150, and 300 ppm GD0-GD20 or PND10	Prenatal CO exposure continuing to PND10 leads to increased concentrations of dopamine but not dopamine metabolites in striatal tissue.	Maternal COHb: 2.5 ± 0.1%, 11.4 ± 0.3%, 18.5 ± 0.5%, 26.8 ± 1.1% (0, 75, 150, and 300 ppm, respectively)
Storm and Fechter (1985, 011653)	Rats	150 ppm GD0-GD20	Prenatal CO exposure increased mean and total cerebellar norepinephrine concentration from PND14 to PND42, but not in the cortex.	
Storm and Fechter (1985, 011652)	Rats	75, 150, and 300 ppm GD0-GD20	CO transiently decreased 5HT and NE in the pons/medulla. CO increased NE in the cortex and hippocampus at PND42. CO dose-dependently reduced cerebellum wet weight.	Maternal COHb: 2.5%, 11.5%, 18.5%, and 26.8% (0, 75, 150, and 300 ppm, respectively)
Storm et al. (1986, 012136)	Rats	75, 150, and 300 ppm GD0-PND10	CO decreased cerebellar weight (150-300 ppm at PND10, 75-300 ppm at PND21) and decreased total cerebellar GABA (150-300 ppm at PND10 and PND21). CO (300 ppm) exposed cerebella has fewer fissures.	Maternal COHb: 2.5%, 11.5%, 18.5%, and 26.8% (0, 75, 150, and 300 ppm, respectively)
Benagiano et al. (2005, 180445)	Rats	75 ppm GD0-GD20	CO reduced the number of GABA and GAD 65/67 positive neuronal bodies and axon terminals in the cerebellar cortex.	
Benagiano (2007, 193892)	Rats	75 ppm GD5-GD20	Adult offspring exposed prenatally to CO exhibited decreased GABA and GAD in the molecular layer and Purkinje neuron layers of the cerebellar cortex	
Antonelli (2006, 194960)	Rats	75 ppm GD5-GD20	CO decreased cortical glutamatergic transmission both at rest and after a chemical depolarizing stimulus.	

Dopaminergic Effects. Dopamine is a catecholamine neurotransmitter that plays an important role in the regulation of male rat sexual behavior. Experiments assessing sexual behavior and mesolimbic dopaminergic function were conducted on adult (5 and 10 mo of age) male offspring gestationally exposed to CO (0, 75 or 150 ppm) (Cagiano et al., 1998, 087170). Maternal COHb at GD10 was 1, 7, and 15% and 1.5, 7, and 16% at GD20 (0, 75, and 150 ppm CO, respectively). At 5 mo of age, CO-exposed male offspring showed decrements in sexual behavior, including an increase in mount-to-intromission latency, a decrease in mount-to-intromission frequency, and a decrease in ejaculation frequency. Further, administration of amphetamine, which stimulates copulatory activity, did not alter CO-induced changes in mount-to-intromission latency or frequency. Basal extracellular dopamine concentration in the nucleus accumbens was unchanged after CO exposure. However, when stimulated with amphetamine administration, control rats had increased release of dopamine that was absent with CO-exposed rats. Rats followed to 10 mo of age showed no significant changes in copulatory activity or neurochemical parameters after CO exposure,

indicating recovery from earlier decrements. This altered male sexual behavior in CO-exposed offspring paralleled earlier studies of mice exposed gestationally to hypoxia (Hermans et al., 1993, 190510). In summary, in utero exposure to CO delayed copulatory sexual behavior in male offspring with accompanying changes in the mesolimbic dopaminergic system.

A second study also found no change in dopamine metabolite levels after prenatal exposure to CO; however, it did find an elevation in dopamine concentration in rats exposed both pre- and postnatally to CO. Exposure of Long Evans rat dams and pups continuously to CO (75, 150, or 300 ppm) with maternal COHb of 11, 19, and 27%, respectively) from conception to PND10 induced significant elevations in dopamine in the striatum at PND21 in CO-exposed offspring versus air exposed controls (Fechter et al., 1987, 012259).

Noradrenergic and Serotonergic Changes. Other monoamine neurotransmitters, norepinephrine (NE) and serotonin (5HT), were tested for sensitivity to CO during development. Long Evans rats exposed to CO (75, 150, or 300 ppm) over the duration of gestation yielded a dose-dependent reduction in cerebellum wet weight (significant at 150 and 300 ppm) at PND21, with increases in NE concentration found in the cortex and hippocampus at PND42 but not PND21 (Storm and Fechter, 1985, 011652). In a separate experiment, CO-exposed (150 ppm) animals presented with increased mean and total NE concentrations in the cerebellum but not cortex when monitored from PND14 to PND42 (Storm and Fechter, 1985, 011653). Also, NE concentration in the pons/medulla decreased linearly with increasing CO exposure at PND21 but not at PND42. A transitory decrease in 5HT concentration was also shown in the pons/medulla after gestational CO exposure (Storm and Fechter, 1985, 011652). Thus, in these studies, it appeared that CO both transiently and permanently altered the pattern of postnatal neurotransmitter development in a region-specific manner and stunted postnatal growth of the cerebellum.

Glutamatergic System. Glutamate is an abundant excitatory neurotransmitter that serves as a precursor for the synthesis of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) catalyzed by glutamic acid decarboxylase (GAD). Primary cell cultures obtained from the cerebral cortex of offspring (PND1) gestationally (GD5-GD20) exposed to CO (75 ppm) had decreased extracellular glutamate (basal and K^+-evoked) levels versus air-exposed controls (Antonelli et al., 2006, 194960). Similarly, CO-exposed (300 ppm only) pups at PND21 had significant decreases in cerebellar GABA content, decreased uptake of exogenous radio-labeled GABA, decreased fissures in the cerebellum, and decreased cerebellum size (Storm et al., 1986, 012136). It is possible this decrease in GABA content is due to a diminished activity of GAD. Rats exposed to CO (75 ppm) in utero (GD0-GD20) exhibited decreased GABA and GAD in the molecular layer and Purkinje neuron layer of the vermian cerebellar cortex (Benagiano et al., 2005, 180445; Benagiano et al., 2007, 193892). This alteration may functionally impair cortical glutamatergic transmission in CO-exposed offspring, possibly affecting learning and memory.

The Developing Auditory System

The developing auditory system of rodents has recently been investigated as a target of CO exposure at levels as low as 12 ppm. The rat brain and auditory system go through extensive cell division and multicellular organization during a major growth spurt in the postnatal period (PND7-PND20), making it a probable target for CO-induced effects. These studies showed that exposure to low concentrations of CO during development can lead to permanent changes in the auditory system that persist into adulthood. Similarly, prenatal exposure to tobacco smoke can cause auditory system deficits as seen in animal tests for auditory responsiveness, habituation, and auditory arousal. Term human infants born to smoking mothers have impaired cochlear development, albeit mild, with decreased amplitudes of transient evoked otoacoustic emissions (OAE) at the highest test frequency (4 kHz) versus newborns born to nonsmokers (Korres et al., 2007, 190908); CO is one of many potential affective components of cigarette smoke.

Table 5-17. Developing auditory system.

Study	Model System	CO Exposure	Response	Notes
DEVELOPING AUDITORY SYSTEM				
Stockard-Sullivan et al. (2003, 190947)	Rats	12-100 ppm 22 h/day PND6 to PND21-PND23	CO (50 ppm) reduced otoacoustic emissions (preneural cochlear function) at 7.13 and 8.01 kHz. CO persistently attenuated the amplitude of the action potential of the eighth cranial nerve (12-50 ppm), persisting to PND73. No functional impairment in the Morris Water Maze after CO exposure.	COHb: 10.2% (100 ppm); 5.5% (AR); 4.1% (MR)
Lopez et al. (2003, 193901)	Rats	12 and 25 ppm PND8-PND22	CO (25 ppm) led to swelling and mild vacuolization of nerve terminals innervating inner hair cells and the fibers of the 8th cranial nerve. CO (25 ppm) decreased expression of neurofilament and myelin basic proteins, cytochrome oxidase, NADH-TR, and calcium ATPase.	
Webber et al. (2003, 190515)	Rats	12.5, 25, 50 ppm PND8 to PND20-PND22	CO decreased c-Fos immunoreactivity in the central inferior colliculus at both PND27 and PND75-PND77 over all dose groups (12.5, 25, or 50 ppm CO)	
Webber et al. (2005, 190514)	Rats	25 and 100 ppm PND9-PND24	CO exposure (25 and 100 ppm) decreased neurofilament proteins, decreased c-Fos expression in the central IC, and increased CuZnSOD in the spiral ganglion neurons. Iron deficiency ablated these responses.	
Lopez et al. (2008, 097343)	Rats	25 ppm 10-18 h/day GD5-20 or GD5-GD20 and PND5-PND20	Prenatal CO exposure led to increased oxidative stress in the cochlear vasculature (high HO-1, SOD-1, iNOS, and nitrotyrosine) and decreased neurofilament proteins and synapsin-1. CO caused morphological deterioration of putative afferent terminals and mild deterioration in the inner hair cells at the basal region of the cochlea.	

Studies on the developing auditory system have used an artificial feeding system where pups were removed from their respective dams and fed a milk substitute comparable to natural rat milk via intragastric cannulation. This allowed nursing pups to be exposed to CO without possible confounding by lactational and maternal CO co-exposure. However, this invasive rat model does cause decreased brain, cerebellum, and lung weight at PND16 in normal air controls. A summary of these studies and others are presented in the above table (Table 5-17).

Using this model, Stockard-Sullivan et al. (2003, 190947) examined Sprague Dawley rat pups receiving low-dose CO (12, 25, or 50 ppm) to determine how perinatal CO exposure (PND6 to PND21-PND23) functionally affected hearing in the developing rat. Rodent pups were either maternally reared (MR), nutritionally supported with the artificial feeding system (AR), or received AR plus CO exposure (ARCO). CO (50 ppm, not 25 ppm) exposure caused significant reductions in distortion product otoacoustic emissions (DPOAE) levels at certain frequencies (7.13 and 8.01 kHz), a measure of preneural cochlear function and thus not affected by eighth cranial nerve function. However, the frequency range where significant CO results were seen is very narrow and low compared to the normal rat audiogram. The eighth cranial nerve, or vestibulocochlear nerve, is responsible for transmitting sound from the inner ear to the brain. This study also found significant attenuation of the action potential (AP) of the eighth cranial nerve with ARCO exposure (12, 25, and 50 ppm CO) versus AR controls at PND22. This is complicated by the finding that AR control animals had significant attenuation of the eighth cranial nerve AP versus MR control animals, implying that artificial rearing contributes to AP changes before CO was introduced. Nonetheless, the CO-dependent attenuation of the eighth cranial nerve AP (versus AR control) was permanent, persisting until adulthood in the 50 ppm CO exposure group (the only CO group monitored). Auditory brain stem response (ABR) conduction time was not affected in CO-exposed animals (12, 25, 50, 100 ppm).These functional tests reported that neonatal exposure to low concentrations of CO can induce auditory functional changes in rodents.

Further studies have investigated physiological changes in cochlear development resulting from chronic CO inhalation. Sprague Dawley rats exposed to low concentrations of CO (12 or 25 ppm, ARCO) from PND6 to PND27 had no evidence of damage to the inner or outer hair cells (Lopez et al., 2003, 193901). However, CO (25 ppm) caused atrophy or vacuolization of the nerve cells that innervate the inner (not outer) hair cells. Also, fibers of the eighth cranial nerve at the level of the internal auditory canal had distorted myelination and vacuolization of the axoplasm after 25 ppm CO exposure. Energy production markers in the organ of corti and spiral ganglion neurons

including cytochrome oxidase (electron transport chain complex IV) and NADH-TR (marker of complex I reductase activity) were significantly decreased after inhalation of 25 ppm (not 12 ppm) CO versus control (AR and MR). Reduced energy production likely led to the decreased expression of the calcium-mediated myosin ATPase and neurofilament proteins in the organ of corti and spiral ganglion neurons (25 ppm CO). Since no changes in body weight were found after CO exposure in these experiments (Stockard-Sullivan et al., 2003, 190947), it is likely that the decreased electron transport chain enzymes are specific to vulnerable areas such as the cochlea.

Further analysis focused attention on CO-induced changes in the inferior colliculus (IC), an auditory integrative section of the midbrain. Low concentrations of CO (12.5, 25, or 50 ppm) inhaled over PND8-PND22 decreased c-Fos immunoreactivity in the central IC at both PND27 and PND75-PND77; immunostaining of other subregions of the IC were not affected by CO (Webber et al., 2003, 190515). c-Fos is an immediate early gene whose tonotopic expression corresponds to neuronal activation in the auditory system. The same decrease in c-Fos expression was seen in rats exposed to 25 or 100 ppm CO from PND9 to PND24 (Webber et al., 2005, 190514). These CO-exposed rats also exhibited decreased neurofilament proteins and increased Cu-Zn superoxide dismutase (SOD1) in the spiral ganglion neurons. This response could be ablated by dietary iron restriction, suggesting an ROS-dependent contribution to the auditory changes seen after CO exposure. These authors postulated that CO creates a persistent oxidative stress condition where ROS generated via the interaction of peroxide and iron (via the Fenton reaction or Haber Weiss chemistry) leads to impaired cochlear development; decreasing the available iron decreases the total pool available for ROS generation. Further, the attenuation of the elevated SOD levels with iron restriction post CO-exposure gives credence to this model.

A recent study has found comparable auditory system responses after prenatal (GD5-GD20) exposure to CO with postnatal exposure (GD5-PND20,) similar to the studies described above (Lopez et al., 2008, 097343). Prenatal CO (25 ppm) exposure led to high levels of the oxidative stress markers HO-1, SOD-1, iNOS, and nitrotyrosine in cochlea vasculature and stria vascularis at PND12; however, unlike postnatally exposed pups, HO-1 and SOD1 levels returned to normal at PND20. Both groups of CO-exposed rats exhibited spiral ganglion cytoplasmic vacuolization, a decrease in type I spiral ganglion neuron neurofilament proteins, thinning and damage in the cells of the stria vascularis, and mild deterioration of the innervation of the inner hair cells. These nerve terminals also had a persistent decrease in synapsin-1, a regulatory neuronal phosphoprotein. These studies suggest that mild chronic CO exposure disrupts the developing auditory system, more often at the IHC innervation and the eighth cranial nerve of the spiral ganglion, possibly by creating an oxidative stress that may be reflected as hearing impairment.

Summary of Toxicological Studies on Developmental Central Nervous System Effects

Toxicological studies employing rodent models have shown that exposure to low concentrations of CO during the in utero or perinatal period can adversely affect adult outcomes including behavior, neuronal myelination, neurotransmitter levels or function, and the auditory system. In utero CO exposure has been shown to impair active avoidance behavior (150 ppm), habituation (75 and 150 ppm), nonspatial memory (75 and 150 ppm), and emotionality (150 ppm). These behavioral changes could be due to neuronal changes or altered neurotransmitter signaling. In utero CO exposure (75 and 150 ppm) was associated with PNS myelination decrements from impaired sphingolipid homeostasis (150 ppm CO). These neuronal changes were also accompanied by electrophysiological changes such as reversible delays in ion channel development and irreversible changes in sodium equilibrium potential (150 ppm). Also, multiple studies demonstrated that in utero CO exposure affected cholinergic (200 ppm), catecholaminergic (200 ppm), noradrenergic (150 ppm), serotonergic (75 ppm), dopaminergic (75 ppm) and glutamatergic (75 ppm), neurotransmitter levels or transmission in exposed rodents. Possible or demonstrated adverse outcomes from the CO-mediated aberrant neurotransmitter levels or transmission include respiratory dysfunction (150 ppm), impaired sexual behavior (150 ppm), and an adverse response to hyperthermic insults resulting in neuronal damage (200 ppm). Finally, perinatal CO exposure has been shown to affect the developing auditory system of rodents, inducing permanent changes into adulthood at concentrations as low as 12 ppm. Together, these animal studies demonstrate that in utero or perinatal exposure to CO can adversely affect adult behavior, neuronal function, neurotransmission, and the auditory system in rodents.

Cardiovascular and Systemic Developmental Effects

In utero exposure to moderate to high concentrations of CO (60, 125, 150, 250, or 500 ppm) is able to induce transient changes in cardiac morphology, cardiac action potentials, and systemic immunity that may make a CO-exposed animal more susceptible to other outside stressors during the immediate neonatal period. Studies of cardiovascular and systemic developmental responses to CO levels of 500 ppm and less are presented below in Table 5-18.

Table 5-18. Cardiovascular and systemic developmental responses.

Study	Model System	CO Exposure	Response	Notes
CARDIOVASCULAR AND SYSTEMIC DEVELOPMENTAL RESPONSES				
Sartiani et al. (2004, 190898)	Rats	150 ppm GD0-GD20	CO delayed action potential duration shortening, decreased the density of I_{to} channels and increased the density of ICa,L channels.	
Prigge and Hochrainer (1977, 012326)	Rats	60, 125, 250, and 500 ppm GD0-GD21	CO depressed fetal hemoglobin (250 and 500 ppm), reduced fetal weight (125, 250, and 500 ppm), decreased hematocrit (250 and 500 ppm), and increased heart weight (60-500 ppm).	
Fechter et al. (1980, 011294)	Rats	150 ppm GD0-GD20	CO transiently increased wet heart weight. There was no increase in dry heart weight.	COHb: 15%
Penney et al. (1982, 011387)	Rats	500 ppm PND1-PND32	CO increased heart weight to body weight ratio, which remained high to PND107. Right ventricular weight was high through PND217. Hydroxyproline and cardiac cytochrome c was depressed but only during CO exposure. Neither lactate dehydrogenase nor myoglobin was altered by CO.	
Styka and Penney (1978, 011166)	Rats	400 or 500 ppm increased to 1,100 ppm Adult 6 wk	CO caused increased heart weight to body weight that regressed within a couple of months after CO exposure.	COHb: 400 ppm-35%; 1,100 ppm-58%
Giustino et al. (1993, 013833)	Rats	75 and 150 ppm GD0-GD20	CO decreased splenic macrophage killing (75 and 150 ppm), phagocytosis (150 ppm), and superoxide release (150 ppm). These alterations were reversible, not seen at PND60.	
Giustino et al. (1994, 076343)	Rats	75 and 150 ppm GD0-GD20	CO (150 ppm) decreased the frequency of splenic leukocyte common antigen (LCA+) cells at PND21 but not PND15 or PND540	COHb: 150 ppm-15%

Myocardial Electrophysiological Maturation

A rat model of in utero exposure was employed to study CO effects on the development of cardiac myocytes. Results demonstrated that in utero CO exposure (150 ppm) alters postnatal cellular electrophysiological maturation in the rat heart (Sartiani et al., 2004, 190898). Specifically, at 4 wk of age, the action potential duration (APD) of isolated cardiac myocytes from CO-exposed animals failed to shorten or mature as the APD of control animals did. Further, the two ion conduction channels I_{to} (transient outward current, K^+-mediated) and ICa,L (L-type Ca^{2+} current), which largely control the rat APD, were significantly different from control animals after in utero CO exposure at 4 wk of age. These CO-dependent changes were resolved by 8 wk of age, reflecting a delayed maturation. Further, these authors postulated that a CO-dependent delay in electrophysiological maturation of the cardiac myocyte (lack of APD shortening) could lead to arrhythmias and thus could be associated with SIDS deaths.

Heart Morphological Changes after In Utero or Perinatal CO Exposure

Multiple authors have reported cardiomegaly following in utero exposure to low concentrations of CO. Prigge and Hochrainer (1977, 012326) reported increased fetal Wistar rat heart wet weight or cardiomegaly following continuous in utero CO (60, 125, 250, and 500 ppm) exposure, with no decreases in near term fetal hematocrit or Hb levels seen at exposures below 250 ppm. Fechter et al. (1980, 011294) found that prenatal exposure to CO affected cardiac development in exposed offspring. Long Evans rats that were exposed to CO continuously

(150 ppm) during gestation manifested with significant elevations in wet heart weight, as well as heart weight in relation to body weight at PND1 but not at PND4, PND14, or PND21. Dry-to-wet weight ratios revealed that the increased heart weight of CO-exposed pups at birth was due to edema or water content. Penney et al. (1982, 011387) studied CO-dependent (500 ppm) cardiomegaly in neonates (continuous CO exposure for 32 days starting at PND1). Other studies of adult male Charles River-derived rats exposed to CO for 6 wk (at 400 or 500 to 1,100 ppm CO), as adults only, developed CO-dependent cardiomegaly during exposure that significantly regressed within a couple of months after termination of CO exposure (Styka and Penney, 1978, 011166).

Systemic Immune Toxicology after In Utero CO Exposure

In utero exposure (GD0-GD20) of male Wistar rats to moderate CO (0, 75, or 150 ppm) concentrations induced reversible changes in macrophage function (Giustino et al., 1993, 013833). The killing of *Candida albicans* (yeast) by splenic macrophages was significantly decreased at PND15 in gestationally CO-exposed male offspring (75 and 150 ppm) but recovered function by PND21. Macrophage phagocytosis of *C. albicans* was significantly reduced at PND15 and PND21 in CO-exposed males (150 ppm only), and recovery was seen at PND60. Superoxide production by the splenic macrophage respiratory burst was significantly decreased at PND15 and PND21 after in utero CO exposure (150 ppm only), with recovery to control levels at PND60. In summary, CO exposure in utero leads to a reversible and concentration-dependent loss of function of splenic macrophages, with decreased killing ability, decreased phagocytosis, and decreased ROS production during the macrophage respiratory burst.

Further studies by the same laboratory showed that in utero exposure of male rats to CO (150 ppm) induced a subtle decrease in the frequency of splenic immunocompetent cells (leukocyte common antigen [LCA+] cells) in a population of splenic immune cells at PND21 but not PND15 or PND540 (Giustino et al., 1994, 076343). Specific LCA+ cell subpopulations, including macrophages, Major Histocompatibility (MHC) II cells, T and B lymphocytes, showed a decreasing trend but were not significant with CO exposure.

Summary of Toxicological Studies of Cardiovascular and Systemic Development

In utero CO exposure is associated with various adverse, albeit nonpersistent, cardiac aberrations. Exposure to 150 ppm induced a delayed maturation of the cardiac action potential in CO-exposed offspring. In other studies, continuous in utero CO exposure (60-500 ppm) induced cardiomegaly at PND1, which was transient and regressed by PND4. CO (75 and 150 ppm) also affects nonspecific immunity, shown through a reversible and dose-dependent loss of function of splenic macrophages, with decreased killing ability, decreased phagocytosis, and decreased macrophage ROS production (150 ppm). Also, the distribution of splenic immunocompetent cells was slightly skewed because of a decrease in the number of LCA+ cells in PND21 male rats exposed during gestation to 150 ppm CO. In conclusion, in utero exposure to moderate doses of CO (60-500 ppm) is able to induce transient changes in cardiac morphology, cardiac action potentials, and systemic nonspecific immunity.

5.4.3. Summary of Birth Outcomes and Developmental Effects

The most compelling evidence for a CO-induced effect on birth and developmental outcomes is for PTB and cardiac birth defects. These outcomes were not addressed in the 2000 CO AQCD (U.S. EPA, 2000, 000907), which included only two studies that examined the effect of ambient CO on LBW. Since then, a number of studies have been conducted looking at varied outcomes, including PTB, birth defects, fetal growth (including LBW), and infant mortality.

There is limited epidemiologic evidence that CO during early pregnancy (e.g., first month and first trimester) is associated with an increased risk of PTB. The only U.S. studies to investigate the PTB outcome were conducted in California, and these reported consistent positive associations with CO exposure during early pregnancy when exposures were assigned from monitors within close proximity of the mother's residential address. Additional studies conducted outside of the U.S. provide supportive, though less consistent, evidence of an association between CO concentration and PTB.

Very few epidemiologic studies have examined the effects of CO on birth defects. Two of these studies found maternal exposure to CO to be associated with an increased risk of cardiac birth defects. Human clinical studies also demonstrated the heart as a target for CO effects (Section 5.2). Animal toxicological studies provided additional evidence for cardiac effects with reported transient cardiomegaly at birth after continuous in utero CO exposure (60, 125, 250 and 500 ppm CO) and delayed myocardial electrophysiological maturation (150 ppm CO). Toxicological studies have also shown that continuous in utero CO exposure (250 ppm) induced teratogenicity in rodent offspring in a dose-dependent manner that was further affected by dietary protein (65 ppm CO) or zinc manipulation (500 ppm CO). Toxicological studies of CO exposure over the duration of gestation have shown skeletal alterations (7 h/day, CO 250 ppm) or limb deformities (24 h/day, CO 180 ppm) in prenatally exposed offspring.

There is evidence of ambient CO exposure during pregnancy having a negative effect on fetal growth in epidemiologic studies. In general, the reviewed studies, summarized in Figure 5-10 through Figure 5-12, reported small reductions in birth weight (~5-20 g). Several studies examined various combinations of birth weight, LBW, and SGA/IUGR, and inconsistent results were reported across these metrics. It should be noted that having a measurable, even if small, change in a population is different than having an effect on a subset of susceptible births and increasing the risk of IUGR/LBW/SGA. It is difficult to conclude if CO is related to a small change in birth weight in all births across the population or a marked effect in some subset of births. Toxicology studies have found associations between CO exposure in laboratory animals and decrements in birth weight (90-600 ppm), as well as reduced prenatal growth (65-500 ppm CO).

In general, there is limited epidemiologic evidence that CO is associated with an increased risk of infant mortality during the neonatal or postneonatal periods. In support of this limited evidence, animal toxicological studies provided some evidence that exogenous CO exposure to pups in utero significantly increased postnatal mortality (7 h/day and 24 h/day, 250 ppm CO; 24 h/day, 90 or 180 ppm CO) and prenatal mortality (7 h/day, 250 ppm CO).

Evidence exists for additional developmental outcomes which have been examined in toxicological studies but not epidemiologic or human clinical studies, including behavioral abnormalities, learning and memory deficits, locomotor effects, neurotransmitter changes, and changes in the auditory system. Structural aberrations of the cochlea involving neuronal activation (12.5, 25 and 50 ppm CO) and auditory related nerves (25 ppm CO) were seen in pups after neonatal CO exposure. Auditory functional testing using otoacoustic emissions testing (OAE at 50 ppm CO) and 8th cranial nerve action potential (AP) amplitude measurements (12, 25, 50, 100 ppm CO) in rodents exposed perinatally to CO showed auditory decrements at PND22 (OAE and AP) and permanent changes in AP into adulthood (50 ppm CO). Furthermore, exogenous CO may interact with or disrupt the normal physiological roles that endogenous CO plays in the body. There is evidence that CO plays a role in maintaining pregnancy, controlling vascular tone, regulating hormone balance, and sustaining normal ovarian follicular maturation.

Overall, there is limited though positive epidemiologic evidence for a CO-induced effect on PTB and birth defects, and weak evidence for a decrease in birth weight, other measures of fetal growth, and infant mortality. Animal toxicological studies provide support and coherence for these effects. Both hypoxic and nonhypoxic mechanisms have been proposed in the toxicological literature (Section 5.1), though a clear understanding of the mechanisms underlying reproductive and developmental effects is still lacking. Taking into consideration the positive evidence for some birth and developmental outcomes from epidemiologic studies and the resulting coherence for these associations in animal toxicological studies, the evidence is **suggestive of a causal relationship between relevant long-term exposures to CO and developmental effects and birth outcomes**.

5.5. Respiratory Effects

5.5.1. Epidemiologic Studies with Short-Term Exposure

This section evaluates the key epidemiologic studies published since the 2000 CO AQCD (U.S. EPA, 2000, 000907) that further examine the association between short-term exposure to CO and respiratory morbidity. Although the number of studies that have specifically examined the CO-respiratory health relationship have increased, there are still considerably less than that for the other criteria air pollutants (e.g., PM and O_3). The epidemiologic studies discussed below represent those studies which (1) were conducted in locations with ambient CO concentrations similar to those in the U.S.; (2) determined to use a reasonable study design and analytical methods; and (3) adequately adjusted for confounding using accepted methods. If limitations in the design or analytical methods used in a study were identified, they were noted. It is recognized that each of the studies evaluated has a varying degree of exposure measurement error due to (1) the number of monitors used within the study, the geographic size of the study area; (2) the spatial variability of CO; and (3) differences in personal exposure distributions in the population; (Section 3.6.8) all of which could influence the associations observed. As a result, in some instances specific details of a study are mentioned to address any potential bias in the reported CO associations. Finally, the issue of confounding by measured or unmeasured copollutants was evaluated, if possible, for each study, through the interpretation of copollutant models. The results from copollutant models were used as an attempt to disentangle the effect of CO from other pollutants while recognizing the high correlation between CO and other combustion-related pollutants.

5.5.1.1. Pulmonary Function, Respiratory Symptoms, and Medication Use

The 2000 CO AQCD (U.S. EPA, 2000, 000907) briefly discussed the potential acute respiratory health effects associated with short-term exposure to CO. An evaluation of the epidemiologic literature at the time did not find any evidence of an association between short-term exposure to CO and lung function, respiratory symptoms, or respiratory disease. As a result, the 2000 CO AQCD (U.S. EPA, 2000, 000907) did not conclude that a causal association exists between short-term exposure to CO and respiratory health effects. Multiple uncertainties were identified in the epidemiologic literature that contributed to this conclusion, which are discussed in Section 5.2.1. The following section evaluates the current literature that examines the potential association between short-term exposure to CO and respiratory health effects. Table 5-19 lists the studies evaluated in this section along with the respiratory health outcomes examined and CO concentrations reported.

Table 5-19. Range of CO concentrations reported in key respiratory morbidity studies that examined effects associated with short-term exposure to CO.

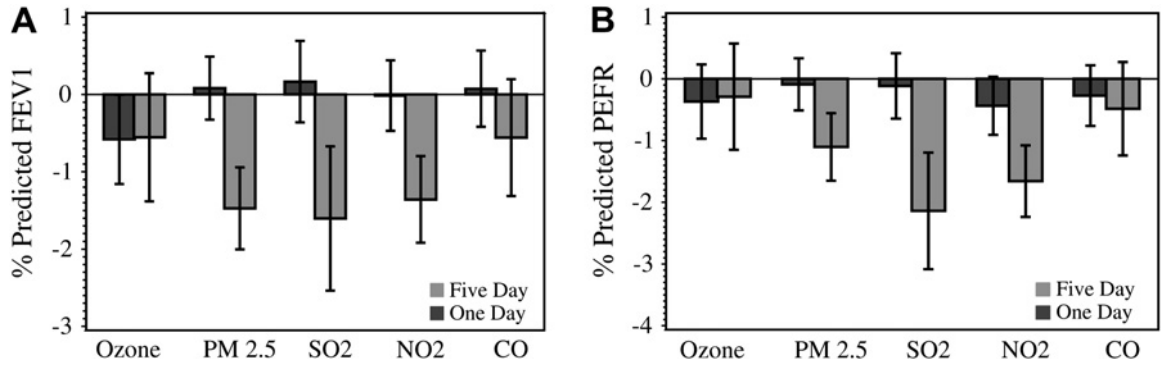
Study	Location Sample Size	Years	Health Outcome	Metric	Mean Concentration (ppm)	Middle/Upper Percentile Concentrations (ppm)
O'Connor et al. (2008, 156818)[b]	7 U.S. cities	8/1998-7/2001	Pulmonary function; Respiratory symptoms	8-h max 24-h avg	NR	8-h max: 50th: 1.2 75th 1.8 99th 3.8 24-h avg: 50th: 0.7 75th 0.9 99th: 1.8
Rabinovitch et al. (2004, 096753)	Denver, CO (Year 1: n = 41) (Year 2: n = 63) (Year 3: n = 43)	11/1999-3/2000; 11/2000-3/2001; 11/2001-3/2002	Pulmonary function; Medication use	24-h avg	1.0	50th: 0.9 75th: 1.2 Maximum: 3.5
Silkoff et al. (2005, 087471)	Denver, CO (Year 1: n = 16) (Year 2: n = 18)	1999-2000 (winter); 2000-2001 (winter)	Pulmonary function; Medication use	24-h avg	1999-2000: 1.2 2000-2001: 1.1	1999-2000 50th: 1.10 75th: 1.43 Maximum: 3.79 2000-2001 50th: 0.975 75th: 1.34 Maximum: 2.81
Fischer et al. (2002, 025731)[a]	The Netherlands (n = 68)	March - April[c]	Pulmonary function	24-h avg	0.80	Max: 1.34
Ranzi et al. (2004, 089500)[a]	Emilia-Romagna Region, Italy (n = 120)	2/1999-5/1999	Pulmonary function; Respiratory symptoms; Medication use	24-h avg	Urban: 1.34 Rural: 1.06	NR
Lagorio et al. (2006, 089800)[a]	Rome, Italy (n = 29)	5/1999-6/1999; 11/1999-12/1999	Pulmonary Function	24-h avg	Spring: 1.83 Winter: 10.7 Overall: 6.4	Overall Max: 25.1
Penttinen et al. (2001, 030335)[a]	Helsinki, Finland (n = 57)	11/1996-4/1997	Pulmonary function	24-h avg	NR	50th: 0.35 75th: 0.43 Maximum: 0.96
Timonen et al. (2002, 025653)[a]	Kuopio, Finland (n = 33)	2/1994-4/1994	Pulmonary function	24-h avg	0.52	Maximum: 2.43
Chen et al. (1999, 011149)	Taiwan (n = 941)	5/1995-1/1996	Pulmonary function	1-h max; 24-h avg	NR	1-h max Maximum: 3.6
Delfino et al. (2003, 050460)	Los Angeles, CA (n = 22)	11/1999-1/2000	Asthma symptoms	1-h max; 8-h max	1-h max: 7.7 8-h max: 5.0	1-h max 90th: 12.0 Maximum: 17 8-h max 90th: 7.9 Maximum: 10
Slaughter et al. (2003, 086294)	Seattle, WA (n = 133)	12/1993-8/1995	Asthma symptoms; Medication use	24-h avg	NR	50th: 1.47 75th: 1.87
Yu et al. (2000, 013254)	Seattle, WA (n = 133)	11/1993-8/1995	Asthma symptoms	24-h avg	1.6	50th: 1.47 Maximum: 4.18
Schildcrout et al. (2006, 089812)	8 North American cities (n = 990)	11/1993-9/1995	Asthma symptoms; Medication use	24-h avg	NR	50th: 0.63-1.49 75th: 0.77-1.90 90th: 0.95-2.40
von Klot et al. (2002, 034706)[a]	Erfurt, Germany (n = 53)	10/1996-3/1997	Asthma symptoms; Medication use	24-h avg	0.78	50th: 0.70 75th: 1.04 Maximum: 2.60

Study	Location Sample Size	Years	Health Outcome	Metric	Mean Concentration (ppm)	Middle/Upper Percentile Concentrations (ppm)
Park et al. (2005, 088673)	Incheon, Korea (n = 64)	3/2002-6/2002	Asthma symptoms; Medication use	24-h avg	Control days: 0.64 Dust days: 0.65	NR
Rodriguez et al. (2007, 092842)	Perth, Australia (n = 263)	6/1996-7/1998	Symptoms associated with respiratory illness	8-h max	1.41	Maximum: 8.03
de Hartog et al. (2003, 001061) [a]	Amsterdam, The Netherlands (n = 37) Erfurt, Germany (n = 47) Helsinki, Finland (n = 47)	1998-1999 (winter)	Respiratory symptoms	24-h avg	Amsterdam: 0.52 Erfurt: 0.35 Helsinki: 0.35	Maximum: Amsterdam: 1.39 Erfurt: 2.17 Helsinki: 0.87

[a]These studies presented CO concentrations in the units mg/m^3. The concentrations were converted to ppm using the conversion factor 1 ppm = 1.15 mg/m^3, which assumes standard atmosphere and ambient temperature.
[b]This study did not present air quality statistics quantitatively, as a result, the air quality statistics presented were estimated from a figure.
[c]This study did not provide the year(s) in which air quality data was collected.

Pulmonary Function

As part of the Inner-City Asthma Study (ICAS), O'Connor et al. (2008, 156818) examined the effect of air pollutants (i.e., $PM_{2.5}$, O_3, NO_2, CO, and SO_2) on lung function in a population of 861 children (5-12 yr old) with persistent asthma in 7 urban U.S. communities. Throughout the study, percent predicted forced expiratory volume in 1 s (FEV_1) and peak expiratory flow (PEF) were examined for each subject during 2-wk periods twice daily every 6 mo for 2 yr. Lung function was examined in single pollutant models using both same-day (lag 0) and 5-day (lag 0-4) ma pollutant concentrations (Figure 5-13). CO was not found to be associated with percent predicted FEV_1 at lag 0, but there was some evidence for a reduction in percent predicted FEV_1 when using the 5-day ma (-0.32 [95% CI: -0.75 to 0.11] per 0.5 ppm increase in 24-h avg CO concentrations). When examining percent predicted PEF, a small reduction was observed at lag 0 (not reported quantitatively), but the effect was found to be slightly larger at lag 0-4 (-0.28 [95% CI: -0.71 to 0.15]). In this study, CO was found to be moderately correlated with other combustion related pollutants (e.g., $PM_{2.5}$ [r = 0.44] and NO_2 [r = 0.54]); however, CO was not included in the multipollutant models examined, limiting the interpretation of the small reductions in lung function observed. Although the observed reductions in lung function did not reach statistical significance, the results do provide some evidence for a potential effect of CO on lung function at relatively low CO concentrations (99th percentile max 8-h avg concentrations: ~ 3.8 ppm).



Source: Reprinted with Permission of Elsevier Ltd. from O'Connor et al. (2008, 156818)

Figure 5-13. Estimated effect (95% confidence intervals) on pulmonary function due to a 10th to 90th percentile increment change in pollutant concentration in single-pollutant models. The estimates shown are from models that included either a 1-day or 5-day avg of pollutant concentration. Effect estimates were adjusted for site, month, site-by-month interaction, temperature, and intervention group in mixed models. Panel A: percent predicted FEV_1 as outcome variable; Panel B: percent predicted PEFR as outcome variable.

The remaining U.S.-based studies evaluated consisted of single-city studies conducted in Denver, CO. Rabinovitch et al. (2004, 096753) examined the association between exposure to ambient air pollutants and asthma exacerbation in a panel of urban minority children, 6-12 yr old, with moderate to severe asthma over three winters. The investigators examined pulmonary function by measuring FEV_1 and PEF in the morning on school days and also at night on weekends or other nonschool days. Using a 3-day ma (lag 0-2) for all pollutants, Rabinovitch et al. (2004, 096753) did not find an association between CO and either lung function parameter during the morning or at night. Silkoff et al. (2005, 087471) also examined lung function during the winter months, but in a panel of former smokers that were at least 40 yr old and had been diagnosed with COPD. In this study, CO concentrations were similar to those reported in Rabinovitch et al. (2004, 096753). The authors examined the association between exposure to air pollutants and lung function (i.e., FEV_1 and PEF) in both the morning and the evening. Silkoff et al. (2005, 087471) found contradictory results when examining the effects of CO for each of the winter periods (1999-2000 and 2000-2001) separately. During the analysis of the first winter (i.e., 1999-2000), CO was not found to be associated with lung function decrements in the morning at any lag, but there was some evidence for lung function decrements during the evening at lag 0. Of note is the increase in FEV_1 during the morning that was observed at lag 1 during this time period. For the second winter (i.e., 2000-2001) the authors found a significant negative association between CO exposure and FEV_1 in the evening at lag 2 and a moderate negative association with PEF at lag 0 in the morning and lag 2 in the evening. Silkoff et al. (2005, 087471) postulated that the difference in the FEV_1 results for the two study periods could be due to higher pollution concentrations along with somewhat lower temperatures and higher humidity in 2000-2001. However, mean CO levels remained relatively constant between the first and second winters, whereas, PM_{10}, $PM_{2.5}$, and NO_2 concentrations all increased. The decrements in FEV_1 observed in the second winter, therefore, may have been due to the slightly worse, although not significantly different, baseline lung function of the panel of subjects used during the second winter (Silkoff et al., 2005, 087471).

In the recent literature, the majority of studies that examined the association between short-term exposure to CO and lung function have been conducted in Europe and Asia. These studies provide some evidence for CO-induced changes in lung function. Negative associations between short-term exposure to CO and lung function were observed primarily in individuals with underlying respiratory conditions; however, some evidence also exists for effects in children that live in urban environments. Penttinen et al. (2001, 030335) examined the association between CO and lung function in a panel consisting of 57 nonsmoking adult asthmatics during the winter and spring in Helsinki, Finland. The authors observed negative associations with PEF (L/min) for a 0.5 ppm increase in 24-h avg CO concentrations in the morning at lag 1 (β = -0.54, SE = 0.084) and in the

afternoon (β = -1.52, SE = 0.29) and evening (β = -1.81, SE = 0.27) for a 5-day avg. In two-pollutant models with daily mean particle number concentration (PNC), CO effects on PEF in the morning were attenuated at lag 1 but remained negative. In addition, negative associations with PEF persisted in the afternoon and evening in the two-pollutant model at lag 0. In this study, moderate correlations between UFPs and other traffic-generated pollutants (e.g., CO [r = 0.44], NO [r = 0.60], and NO_2 [r = 0.44]) make it difficult to attribute the observed respiratory effects to a specific pollutant.

Lagorio et al. (2006, 089800) also conducted a study that examined the association between CO and lung function in adults. In this study, three panels of subjects with underlying asthma, COPD, or IHD, who resided in Rome, Italy, were selected. The ages of the subjects varied depending on the panel, but overall the subjects ranged from 18-80 yr old. In single-pollutant models with CO, a reduction in forced vital capacity (FVC) and FEV_1 was observed at most of the lags examined (i.e., 0, 0-1, and 0-2) for both the COPD and asthma panels. No association was observed between CO and FVC or FEV_1 in the IHD panel. Lagorio et al. (2006, 089800) did observe a relatively high correlation between CO and $PM_{2.5}$ but not NO_2 (r = 0.05). Copollutant models were not conducted in this analysis to identify whether the CO associations observed are potentially confounded by other pollutants.

Studies that focused on alterations in lung function in asthmatic children reported results consistent with those observed in adult asthmatics. Timonen et al. (2002, 025653) examined the effect of CO on bronchial responsiveness and pulmonary function (i.e., FVC, FEV_1, MMEF, and AEFV) at rest and after exercise in a panel of children, 7-12 yr old with chronic respiratory symptoms, during the winter in Kuopio, Finland. The authors found that CO was significantly associated with decrements in baseline lung function (i.e., lung function measured prior to exercise) for FVC (mL) at lags 2 (-17.5 mL), 3 (-24.8 mL), and 4-day avg (-52.5 mL), and for FEV_1 (mL) at lag 3 (-20.9 mL), for a 0.5 ppm increase in 24-h avg CO concentration. CO was not found to be associated with exercise-induced changes in lung function or bronchial responsiveness. Overall, Timonen et al. (2002, 025653) found that increased concentrations of combustion-related byproducts (i.e., BS, PM_{10}, particle numbers, NO_2, and CO) was associated with impairment in baseline lung function. These associations, along with the high correlation between CO and combustion-related pollutants (e.g., PM_{10} [r = 0.64]; NO_2 [r = 0.88]), contributed to the inability of the authors to conclude that the lung function effects observed were due to biological changes in lung pathology specific to CO exposure.

Chen et al. (1999, 011149) examined the effect of CO on lung function in 941 8- to 13-yr-old asthmatic children in Taiwan. The authors observed an association between short-term exposure to CO and decrements in FVC (mL) at a 2-day lag when using daytime average CO concentrations (from 8:00 a.m. to 6:00 p.m.) in a single-pollutant model. However, the authors found a high correlation between CO and NO_2 concentrations (r = 0.86-0.98), and did not conduct copollutant analyses.

An additional study, Fischer et al. (2002, 025731), examined the association between CO and respiratory health, specifically lung function in a cohort study of 68 children ages 10-11 yr who lived in an urban environment (Utrecht, The Netherlands). In this study, the authors examined whether eNO was a more sensitive measure of lung damage than the traditional pulmonary function measurements (i.e., FVC, FEV_1, PEF, and MMEF). Fischer et al. (2002, 025731) found negative associations between CO and FEV_1, PEF, and MMEF at both lags 1 and 2, as well as an association between CO and an increase in eNO at lag 1. However, the study did not provide pollutant correlations or examine copollutant models, limiting the interpretation of these results.

Respiratory Symptoms in Asthmatic Individuals

Upon evaluating the literature that examined the association between short-term exposure to CO and respiratory symptoms in asthmatic individuals, consistent, positive associations were observed across studies. The studies evaluated that included children enrolled in the Childhood Asthma Management Program (CAMP) study found that CO was positively associated with asthma symptoms. Yu et al. (2000, 013254) found a 1.14-fold increase in asthma symptoms ([95% CI: 1.05-1.23] per 0.5 ppm increase in 24-h avg CO) at lag 1 in a population of 5- to 13-yr-old asthmatic children (n = 133) in Seattle, WA. Similar effects were observed at lag 0 and lag 2. These effects persisted when controlling for previous day's asthma symptoms at all lags, with the largest effect at lag 1 (OR=1.12 [95% CI: 1.05-1.19]) and in multipollutant models with $PM_{1.0}$ and SO_2.

Using the same population of children, Slaughter et al. (2003, 086294) found an association between short-term exposure to CO at lag 1 and asthma severity both with and without controlling for the previous day's asthma severity, (RR = 1.04 [95% CI: 1.01-1.08] and RR = 1.03 [95% CI: 1.00-1.05] per 0.5 ppm increase in 24-h avg CO, respectively). However, this study only examined the effect of copollutant models on PM risk estimates, not CO. Schildcrout et al. (2006, 089812) examined the association between air pollutants and asthma symptoms in 990 children ages 5-12 yr in 8 North American cities. The authors found a positive association between short-term exposure to CO and asthma symptoms at lag 0 (OR = 1.04 [95% CI: 1.00-1.07] per 0.5 ppm increase in 24-h avg CO), but similar effects were also observed at lag 1, 2, and the 3-day moving sum. The CO effects observed persisted when NO_2, PM_{10}, and SO_2 where included in joint-pollutant models.

As previously mentioned, O'Connor et al. (2008, 156818) conducted an additional multicity study to examine the effect of air pollutants (i.e., $PM_{2.5}$, O_3, NO_2, CO, and SO_2) on respiratory health in a population of 861 children (5-12 yr) with persistent asthma in 7 U.S. urban communities. The authors collected information on asthma symptoms every 2 mo and examined the association between a 2-wk recall of the asthma symptoms and each air pollutant. O'Connor et al. (2008, 156818) used a 19-day lag, which encompassed the 14 days of the symptom recall period and the 5-day lag period proceeding the symptom recall period. In a single-pollutant model, CO was significantly associated with number of days with a wheeze-cough (14% [95% CI: 2-29]), number of nights with asthma symptoms (i.e., nighttime asthma) (19% [95% CI: 4-36]), and number of days a child slowed down or stopped play (15% [95% CI: 2-30]) per 0.5 ppm increase in 24-h avg CO concentrations during the 2-wk recall period. In this study, CO effects were not examined in a copollutant model.

U.S.-based single-city studies also found positive associations between CO and asthma symptoms (Delfino et al., 2003, 050460; Rabinovitch et al., 2004, 096753). Rabinovitch et al. (2004, 096753) found evidence for an increase in asthma exacerbations in response to 24-h avg CO concentrations for a 3-day ma (lag 0-2) (OR = 1.02 [95% CI: 0.89-1.16] per 0.5 ppm increase in 24-h avg CO) in a population of urban poor children with moderate to severe asthma in Denver, CO. Delfino et al. (2003, 050460) also reported evidence of a positive association between CO and asthma symptoms (based on symptoms that interfere with daily activities) using a population of Hispanic children with asthma in a Los Angeles, CA, community. However, Delfino et al. (2003, 050460) only found positive associations at 1-day lags when using either the 1-h max (OR=1.05 [95% CI: 0.88-1.26] per 1 ppm increase in 1-h max CO concentrations) or max 8-h avg (OR=1.09 [95% CI: 0.80-1.50] per 0.75 ppm increase in max 8-h avg CO concentrations) CO concentration as the exposure metric. It should be noted that in comparison to Rabinovitch et al. (2004, 096753) and the other respiratory symptoms studies discussed above, the mean ambient concentrations for 1-h max and max 8-h avg reported by Delfino et al. (2003, 050460) were 7.7 ppm and 5.0 ppm, respectively, both of which are approximately 3.5 times higher than the corresponding 24-h avg concentrations reported in the other studies.

In addition to the U.S.-based studies presented above, international studies were evaluated that examined the association between short-term exposure to CO and asthma symptoms in study populations that included adults. Figure 5-14 summarizes the results from studies that provided comparable quantitative results and examined the association between short-term exposure to CO and asthma or respiratory symptoms in asthmatic individuals. A panel study consisting of 53 adults with asthma or asthma symptoms in Germany (Von et al., 2002, 034706) observed a marginal association between CO concentration and the prevalence of wheezing at lag 0 (OR = 1.03 [95% CI: 0.97-1.08] per 0.5 ppm increase in 24-h avg CO), and a positive association for a 5-day mean concentration (OR = 1.12 [95% CI: 1.05-1.21] per 0.5 ppm increase in 24-h avg CO). However, the authors found CO to be highly correlated with UFPs (r = 0.66), complicating the interpretation of the associations observed. Additionally, Park et al. (2005, 088673) in a panel study of individuals 16-75 yr old in Incheon, Korea, with bronchial asthma, did not find an association between CO and nighttime asthma symptoms or cough.

To further examine the effect of CO on asthma and asthma symptoms, some studies also analyzed medication use in asthmatic individuals in response to an increase in air pollutant concentrations. The majority of U.S.-based studies (i.e., Rabinovitch et al., 2004, 096753; Schildcrout et al., 2006, 089812; Slaughter et al., 2003, 086294) focused on rescue inhaler use in children with ages ranging from 5 to13 yr. Rabinovitch et al. (2004, 096753) found a weak association (OR = 1.08 [95% CI: 1.00-1.17] per 0.5 ppm increase in 24-h avg CO) between rescue inhaler use in a population of 6- to 12-yr old urban minority children with moderate to severe asthma

in the winter in Denver, CO. In a population of 5- to 12-yr-old children with asthma in Seattle, WA, Slaughter et al. (2003, 086294) found a stronger association with rescue inhaler use both with and without taking into consideration the previous day's asthma severity, (RR: 1.04 [95% CI: 1.01-1.08] per 0.5 ppm increase in 24-h avg CO) and (RR: 1.03 [95% CI: 1.00-1.05] per 0.5 ppm increase in 24-h avg CO), respectively. Similar results were observed in a multicity study conducted by Schildcrout et al. (2006, 089812) which analyzed rescue inhaler use in 990 children ages 5-13 yr with asthma in 8 North American cities. Schildcrout et al. (2006, 089812) found that short-term exposure to CO was positively associated with rescue inhaler use at lags of 0, 2, and a 3-day moving sum, and that the association was fairly robust to a simultaneous increase in CO and other pollutants (i.e., NO_2, PM_{10}, and SO_2) in joint models. Overall, Slaughter et al. (2003, 086294) and Schildcrout et al. (2006, 089812) question the associations observed due to the lack of biological plausibility for CO-induced respiratory effects and the high correlation between CO and NO_2 (which suggests that other pollutants from mobile sources are driving the associations observed), respectively. Additional studies (Park et al., 2005, 088673; Silkoff et al., 2005, 087471; Von et al., 2002, 034706) conducted in Denver, CO; Erfurt, Germany; and Incheon, Korea, respectively, found associations between CO and medication use that are consistent with those previously reported, but in populations with combined ages ranging from 16 to 77 yr. Figure 5-14 presents the risk estimates from studies that examined the association between short-term exposure to CO and medication use in asthmatic individuals.

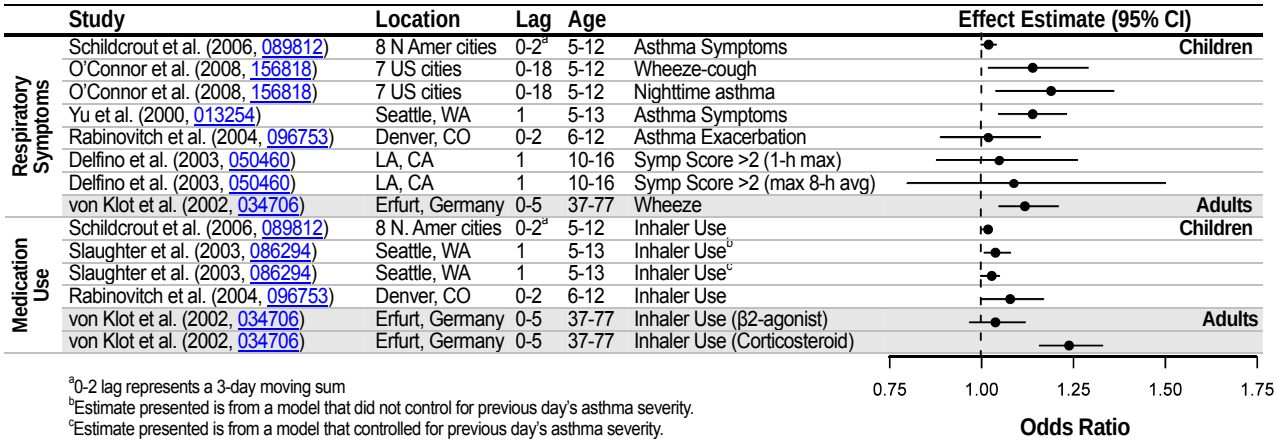


Figure 5-14. Summary of associations for short-term exposure to CO and asthma symptoms, respiratory symptoms and medication use in asthmatic individuals.[1] Effect estimates were standardized depending on the averaging time used in the study: 0.5 ppm for 24-h avg, 0.75 ppm for max 8-h avg, and 1.0 ppm for 1-h max.

Respiratory Symptoms in Nonasthmatic Individuals

In addition to examining the association between short-term exposure to CO and respiratory symptoms (e.g., cough, wheeze, shortness of breath) in asthmatic populations, some studies examined respiratory effects in individuals classified as nonasthmatics. Rodriguez et al. (2007, 092842) examined the effect of CO on respiratory symptoms in a panel of 263 children 0- to 5-yr old at high risk for developing asthma in Perth, Australia. Rodriguez et al. (2007, 092842) found CO concentrations to be positively associated with wheeze/rattle chest and runny/blocked nose at both a 5-day lag and a 0-5-day lag. In this study, copollutant models were not examined, CO correlations with other pollutants were not presented, and additional analyses were not conducted to further characterize the associations observed.

[1] Effect estimates from Park et al. (2005, 088673) were not included in this figure because the study did not provide the increment at which the effect estimates were calculated. Additionally, estimates for Silkoff et al. (2005, 087471) were not included in the figure because results were not presented quantitatively.

In a panel of individuals ≥ 50 yr of age with CHD in three European locations (Amsterdam, The Netherlands; Erfurt, Germany; and Helsinki, Finland) during the winter, de Hartog et al. (2003, 001061) observed some marginal associations, specifically between CO concentration and the incidence of the respiratory symptoms shortness of breath and phlegm at lag 3, OR=1.17 (95% CI: 0.96-1.40) and OR=1.22 (95% CI: 0.93-1.57), respectively, per 0.5 ppm increase in 24-h avg CO concentrations. However, the authors found that the associations between air-pollution exposure and respiratory symptoms were stronger for $PM_{2.5}$ than for gaseous air pollutants. Overall, the associations observed in this study should be viewed with caution because the panel consisted of individuals on a variety of daily medications (i.e., beta blockers, ACE inhibitor + AT blocker, calcium antagonist, aspirin, digitalis, inhaled beta-agonist, and nitroglycerin).

Summary of Associations between Short-Term Exposure to CO and Pulmonary Function, Respiratory Symptoms, and Medication Use

A limited body of evidence is available that examined the effect of short-term exposure to CO on various respiratory health endpoints. Specifically, among asthmatics, the studies reviewed generally found positive associations between short-term exposure to CO and respiratory-related health effects (i.e., decrements in lung function, respiratory symptoms, and medication use). On-road vehicle exhaust emissions are a nearly ubiquitous source of combustion pollutant mixtures that include CO and can be an important contributor to CO-related health effects in near-road locations, which is evident by the high correlations reported between CO and other combustion-related pollutants (i.e., NO_2 and PM). However, the limited number of copollutant analyses among this group of studies complicates the efforts to disentangle the health effects attributed to CO from the larger traffic-related pollutant mix. Additional uncertainty exists as to a biologically plausible mechanism that could explain the effect of CO on respiratory health.

5.5.1.2. Respiratory Hospital Admissions, ED Visits and Physician Visits

The 2000 CO AQCD (U.S. EPA, 2000, 000907) evaluated a limited amount of literature that examined the association between short-term exposure to CO and respiratory hospital admissions (HAs), ED visits, and physician visits in the U.S. (i.e., Seattle, WA; Reno, NV; and Anchorage, AK) and Europe (i.e., Barcelona, Spain). From these studies, the 2000 CO AQCD (U.S. EPA, 2000, 000907) concluded that positive associations were observed for short-term exposure to CO with several respiratory outcomes, including asthma and COPD. However, the lack of a biologically plausible mechanism for CO-induced respiratory morbidity at that time brought into question whether the results observed could be attributed to CO independently of other pollutants in the air pollutant mixture. Additional uncertainties were identified in the epidemiologic literature that contributed to this conclusion, which were discussed in Section 5.2.1.

This section evaluates those studies published since the 2000 CO AQCD (U.S. EPA, 2000, 000907) that examined the association between short-term exposure to CO at ambient concentrations similar to those found in the U.S. and respiratory-related HAs (Figure 5-15), ED visits (Figure 5-16), and physician visits. Unlike previous sections, which also evaluated studies conducted outside of North America, the expansive number of studies conducted in the U.S. and Canada provide adequate evidence to examine the association between short-term exposure to CO and respiratory HAs and ED visits. Although not discussed in this section, collectively, the studies conducted outside of the U.S. observed associations that are consistent with those observed in the U.S.- and Canadian-based studies evaluated below (see Annex C for results from the international studies evaluated).

Overall, this section focuses on respiratory-related HAs because the majority of the literature examines HAs as opposed to ED visits or physician visits (Table 5-20 presents the studies evaluated in this section along with the range of CO concentrations measured in each study). It must be noted that when examining the association between short-term exposure to CO and health outcomes that require medical attention, it is important to distinguish between HAs, ED visits, and physician visits for respiratory outcomes (more so than for cardiovascular outcomes). This is because it is likely that a small percentage of respiratory ED visits will be admitted to the hospital and, therefore, may represent potentially less serious but more common outcomes. To adequately distinguish between the results presented in HAs, ED visit, and physician visit studies, each outcome is evaluated in individual sections. In addition, each section presents results separately for respiratory health

outcomes which include all respiratory diagnoses (ICD-9: 460-519) or selected diseases (e.g., asthma, COPD, pneumonia and other respiratory infections) in order to evaluate the potential effect of short-term exposure to CO on each outcome.

Table 5-20. Range of CO concentrations reported in key respiratory HA and ED visit studies that examine effects associated with short-term exposure to CO.

Study	Location	Type of Visit (ICD9)	Metric	Mean Concentration (ppm)	Middle/Upper Percentile Concentrations (ppm)
Cakmak et al. (2006, 093272)	10 Canadian cities	Hospital Admissions: Respiratory disease (i.e., Acute bronchitis and bronchiolitis; pneumonia; chronic and unspecific bronchitis; emphysema; asthma; bronchiectasis; chronic airway obstruction)	24-h avg	0.8	Maximum: 6.5
Linn et al. (2000, 002839)	Los Angeles, CA	Hospital Admissions: Pulmonary; asthma; COPD	24-h avg	Winter: 1.7; Spring: 1.0; Summer: 1.2; Fall: 2.1	Maximum: Winter: 5.3; Spring: 2.2; Summer: 2.7; Fall: 4.3;
Slaughter et al. (2005, 073854)	Spokane, WA	ED Visits and Hospital Admissions: Respiratory; asthma; COPD; pneumonia; acute respiratory infection	24-h avg	Hamilton St.: 1.73 Backdoor Tavern: 1.29 Spokane Club: 1.41 Third and Washington: 1.82 Rockwood: 0.42	95th: 3.05
Burnett et al. (2001, 093439)	Toronto, ON, Can	Hospital Admissions: Respiratory disease (i.e., asthma; acute bronchitis/bronchiolitis; croup; pneumonia)	1-h max	1.9	50th: 1.8; 75th: 2.3; 95th: 3.3; 99th: 4.0 Maximum: 6.0
Yang et al. (2003, 055621)	Vancouver, BC, Can	Hospital Admissions: Respiratory diseases	24-h avg	0.98	50th: 0.82; 75th: 1.16 Maximum: 4.90
Lin et al. (2003, 042549)	Toronto, ON, Can	Hospital Admissions: Asthma	24-h avg	1.18	50th: 1.10; 75th: 1.40 Maximum: 6.10
Lin et al. (2004, 055600)	Vancouver, BC, Can	Hospital Admissions: Asthma	24-h avg	0.96	50th: 0.80; 75th: 1.12 Maximum: 4.90
Moolgavkar (2003, 042864)	Cook County, IL; Los Angeles County, CA	Hospital Admissions: COPD	24-h avg	NR	Cook: 50th: .99; 75th: 1.25 Maximum: 3.91 Los Angeles: 50th: 1.35; 75th: 2.16 Maximum: 5.96
Yang et al. (2005, 090184)	Vancouver, BC, Can	Hospital Admissions: COPD	24-h avg	0.71	50th: 0.64 Maximum: 2.48
Karr et al. (2006, 088751)	South Coast Air Basin, CA	Hospital Admissions: Acute bronchiolitis	24-h avg	Lag 1: Index: 1.730 Referent: 1.750 Lag 4: Index: 1.760 Referent: 1.790	Lag 1: Index: 50th: 1.52; 75th: 2.26; 90th: 3.16 Maximum: 9.60 Referent: 50th: 1.51; 75th: 2.29; 90th: 3.23 Maximum: 9.60 Lag 4: Index: 50th: 1.54; 75th: 2.31; 90th: 3.23 Maximum: 8.71 Referent: 50th: 1.55; 75th: 2.35; 90th: 3.30 Maximum: 9.60

Study	Location	Type of Visit (ICD9)	Metric	Mean Concentration (ppm)	Middle/Upper Percentile Concentrations (ppm)
Karr et al. (2007, 090719)	South Coast Air Basin, CA	Hospital Admissions: Acute bronchiolitis	24-h avg; Monthly avg	24-h avg: 1.720 Monthly: 1.770	24-h avg: 50th: 1.61; 75th: 2.08; 90th: 2.75 Maximum: 5.07 Monthly avg: 50th: 1.63; 75th: 2.13; 90th: 2.88 Maximum: 8.30
Zanobetti and Schwartz (2006, 090195)	Boston, MA	Hospital Admissions: Pneumonia	24-h avg	NR	50th: 0.48; 75th: 0.60; 95th: 0.88
Lin et al. (2005, 087828)	Toronto, ON, Canada	Hospital Admissions: Respiratory infections	24-h avg	1.16	50th: 1.05; 75th: 1.37 Maximum: 2.45
Peel et al. (2005, 056305)	Atlanta, GA	ED Visits: All respiratory; asthma; COPD; URI; pneumonia	1-h max	1.8	90th: 3.4
Tolbert et al. (2007, 090316)	Atlanta, GA	ED Visits: Respiratory diseases (i.e., asthma; COPD; URI; pneumonia; bronchiolitis)	1-h max	1.6	50th: 1.3; 75th: 2.0; 90th: 3.0 Maximum: 7.7
Ito et al. (2007, 156594)	New York, NY	ED Visits: Asthma	8-h max	1.31	50th: 1.23; 75th: 1.52; 95th: 2.11
Villeneuve et al. (2006, 091179)	Toronto, ON, Canada	Physicians Visits: Allergic rhinitis	24-h avg	1.1	Maximum: 2.2
Sinclair et al. (2004, 088696)	Atlanta, GA	Urgent Care Visits: Asthma; respiratory infections	1-h max	1.3	NR

Hospital Admissions

Respiratory Disease

The majority of studies from North America that examined the association between short-term exposure to CO and HAs for all respiratory diseases were conducted in Canada, and only one of these studies presented results from a combined analysis of multiple cities (Cakmak et al., 2006, 093272). In a study of 10 of the largest Canadian cities, Cakmak et al. (2006, 093272) examined respiratory HAs (ICD-9: 466, 480-486, 490-494, 496) in relation to ambient gaseous pollutant concentrations for the time period 1993-2000. This study reported a 0.37% (95% CI: 0.12-0.50) increase in respiratory hospital admissions for all ages for a 0.5 ppm increase in 24-h avg CO (lag 2.8 days averaged over the 10 cities[1]). However, Cakmak et al. (2006, 093272) only examined the potential confounding effects of gaseous pollutants (i.e., NO_2, SO_2, and O_3) on the CO risk estimate in a multipollutant model and did not provide correlation coefficients, limiting the interpretation of the effects observed in the single-pollutant model. U.S.-based studies (Los Angeles and Spokane) that examined HAs for all respiratory diseases reported similarly weak or null associations with CO (Linn et al., 2000, 002839; Slaughter et al., 2005, 073854). But two single-city studies conducted in Canada reported stronger associations, primarily through evidence from copollutant models, between short-term exposure to CO and respiratory disease HAs (Burnett et al., 2001, 093439; Yang et al., 2003, 055621). In a study conducted in Toronto, Canada, for the time period 1980-1994, Burnett et al. (2001, 093439) reported a relatively strong association between 1-h max CO and respiratory disease HAs in children <2 yr of age for the diagnoses of asthma (493), acute bronchitis/bronchiolitis (466), croup (464.4), and pneumonia (480-486). The authors found a 9.7% (95% CI: 4.1-15.5) increase in HAs for a 2-day avg (lag 0-1) per 1 ppm increase in 1-h max CO. In the two-pollutant model analysis with O_3, the estimate for CO remained elevated (7.29% [95% CI: 1.75-13.1]), but CO

[1] To determine the lag for the combined estimate across all 10 cities, Cakmak et al. (2006, 093272) averaged the strongest associations from lags 0-5 days from each city.

was not found to be highly correlated with O_3 (r = 0.24). Yang et al. (2003, 055621) reported similar results (OR = 1.04 [95% CI: 1.01-1.06] at lag 1 per 0.5 ppm increase in 24-h avg CO) for pediatric (<3 yr of age) respiratory disease (ICD-9: 460-519) HAs in Vancouver for the time period 1986-1998. Yang et al. (2003, 055621) also reported elevated associations with 24-h avg CO and respiratory HAs (ICD-9: codes 460-519) for ages 65 yr and over in Vancouver, Canada, (OR = 1.02 [95% CI: 1.00-1.04]) at lag 1 for a 0.5 ppm increase in 24-h avg CO. The authors found that the CO risk estimates remained the same when O_3 was included in the model, which could be attributed to the lack of collinearity between CO and O_3 due to their negative correlation (r = -0.52).

Asthma

Some studies that examined the effect of short-term exposure to CO on asthma HAs conducted all age and age-stratified analyses, specifically to examine effects in children. In a few studies conducted in Canada, evidence was observed for increased pediatric (ages 6-12 yr) asthma HAs (ICD-9: 493) in boys but not girls (Lin et al., 2003, 042549; Lin et al., 2004, 055600); however, a biological explanation was not provided which could explain this difference. Lin et al. (2003, 042549) used a bidirectional case-crossover analysis in Toronto, Canada, for the years 1981-1993. The authors reported an OR of 1.05 (95% CI: 1.00-1.11) per 0.5 ppm increase in 24-h avg CO for a 1-day lag for boys, with similar results being reported when averaging CO concentrations up to 7 days prior to an HA. Risk estimates for girls did not provide evidence of an association using the same lag structure that was used in the boys' analysis (OR = 1.00 [95% CI: 0.93-1.06]); lag 1). In this study, CO levels were moderately correlated with NO_2 (r = 0.55) and $PM_{2.5}$ (r = 0.45), and weakly correlated with SO_2 (r = 0.37). In this study, copollutant analyses were not conducted to examine the potential confounding effect of different PM size fractions or gaseous pollutants on CO risk estimates. It should be noted that this study used a bidirectional case-crossover analysis, which may bias the results in either direction (Levy et al., 2001, 017172). Studies that examined the various referent selection strategies for the case-crossover study design have concluded that the preferred control selection strategy is the time-stratified framework (Levy et al., 2001, 017172). Lin et al. (2004, 055600) also examined the association between air pollutants and asthma HAs in children, but using a time-series study design in Vancouver during the years 1987-1998. In this study, the authors stratified results by socioeconomic status (SES) and found some evidence for an association between CO and asthma HAs for both girls and boys, of both high and low SES at lag 1 (RR=1.01-1.06 per 0.5 ppm increase in 24-h avg CO); but overall, the evidence was less consistent for a greater effect in boys versus girls compared to Lin et al. (2003, 042549). In a study that examined asthma HAs for all ages and genders combined, Slaughter et al. (2005, 073854) observed some evidence for an increase in asthma HAs (ICD-9 493) in Spokane (1995-2000) for CO at lag 2 (RR = 1.03 [95% CI: 0.98-1.08]) for a 0.5 ppm increase in 24-h avg CO but not for the other two lags examined (lag 1 and lag 3).

Chronic Obstructive Pulmonary Disease

A few of the studies examined the effect of short-term exposure to CO on COPD, or obstructive lung disease, and HAs. Moolgavkar (2003, 042864) (a reanalysis of Moolgavkar, 2000, 010274) examined HAs for COPD plus "allied diseases" (ICD-9 490-496) in two U.S. counties (Cook County, IL, and Los Angeles County, CA) for the years 1987-1995, using Poisson generalized linear models (GLMs) or generalized additive models (GAM), with the more stringent convergence criteria. Overall, the results from both models were similar. Using the GAM models, the study reported increases in HAs of 0.53-1.20% for all ages in Los Angeles County and 0.17-1.41% for ages ≥ 65 yr in Cook County, for a 0.5 ppm increase in 24-h avg CO and lags ranging from 0 to 5 days. However, CO was found to be highly correlated with NO_2 in both Cook County (r = 0.63) and Los Angeles County (r = 0.80), but Moolgavkar (2003, 042864) did not examine the influence of copollutants on CO risk estimates. Yang et al. (2005, 090184) reported similar results for COPD HAs (ICD-9 490-492, 494, 496) in Vancouver for ages ≥ 65 yr for the years 1994-1998 for a ma of 0- to 6-day lags (RR = 1.14 [95% CI: 1.03-1.23] per 0.5 ppm increase in 24-h avg CO). In this study, CO concentrations were moderately correlated with NO_2, SO_2, and PM_{10}, and moderately negatively correlated with O_3. In copollutant models, Yang et al. (2005, 090184) found that risk estimates for CO and COPD HAs remained elevated with O_3 (RR=1.19 [95% CI: 1.07-1.32]) or SO_2 (RR=1.19 [95% CI: 1.02-1.39]), but were attenuated when adjusting for NO_2 (RR=1.07 [95% CI: 0.92-1.24]) or PM_{10} (RR=1.03 [95% CI: 0.89-1.21]). Contrary to Moolgavkar (2003, 042864) and Yang et al.

(2005, 090184), Slaughter et al. (2005, 073854) found no association between short-term exposure to CO and COPD HAs (ICD-9 491, 492, 494, 496) in Spokane, WA, at lag 1-day (RR = 0.97 [95% CI: 0.93-1.01] per 0.5 ppm increase in 24-h avg CO) with similar results being reported for 2- and 3-day lags. However, this study did not examine correlations between CO and other gaseous pollutants or conduct copollutant analyses.

Acute Bronchiolitis in Infants

Karr et al. (2006, 088751; 2007, 090719) examined both short-term (lag 0 or 1) and longer term levels of CO in relation to acute bronchiolitis (ICD-9: 466) HAs during the first year of life from 1995-2000 in the South Coast Air Basin in California. Karr et al. (2006, 088751) found no evidence of a short-term association between ambient CO concentrations and HAs for acute bronchiolitis at lag 1 day (OR= 0.99 [95% CI: 0.98-1.01] per 0.5 ppm increase in 24-h avg CO). In addition, Karr et al. (2007, 090719), which examined longer term exposures (average in the month prior to a HA and lifetime average) in a matched case-control study, did not provide any evidence of an association with CO. Neither of these studies examined the correlation between CO and other pollutants nor conducted copollutant analyses.

Pneumonia and Other Respiratory Infections

In addition to examining the effect of short-term exposure to CO on health outcomes that can limit the function of the respiratory system, some studies examined the effect of CO on individuals with pneumonia (ICD-9: 480-486) separately or in combination with other respiratory infections. Zanobetti and Schwartz (2006, 090195) examined pneumonia HAs (ICD-9 480-487) in Boston, MA, for the years 1995-1999 for individuals ages 65 yr and older, using a time-stratified case-crossover analysis. The authors reported an increase in pneumonia HAs at lag 0 of 5.4% (95% CI: 1.2-10.0) per 0.5 ppm increase in 24-h avg CO. While Zanobetti and Schwartz (2006, 090195) did not report multipollutant results, they suggested that CO was most likely acting as a marker for traffic-related pollutants because CO was highly correlated with both BC (r = 0.80) and NO_2 (r = 0.67) and moderately correlated with $PM_{2.5}$ (r = 0.52). Instead of examining the effect of CO on pneumonia HAs separately, as was done by Zanobetti and Schwartz (2006, 090195), Lin et al. (2005, 087828) presented results for the overall effect of CO on respiratory infection HAs (ICD-9: 464, 466, 480-487). In this analysis, Lin et al. (2005, 087828) examined the potential increase in respiratory HAs in children <15 yr of age in Toronto, Canada, for 1998-2001, using a bidirectional case-crossover approach. The authors reported elevated estimates for boys (OR=1.17 [95% CI: 1.03-1.32] per 0.5 ppm increase in 24-h avg CO for a 6-day ma) while the estimate for girls was weaker and with wider confidence intervals (OR=1.06 [95% CI: 0.91-1.23]). In multipollutant models with both $PM_{2.5}$ and $PM_{10-2.5}$ the CO risk estimates were slightly attenuated but remained positive (boys: OR=1.10 [95% CI: 0.96-1.26]; girls: OR=1.03 [95% CI: 0.88-1.06]). Lin et al. (2005, 087828) did not provide an explanation as to why the estimates were stronger for boys than for girls. It should be noted that this study used a bidirectional case-crossover analysis, which, as discussed previously, may bias the results in either direction (Levy et al., 2001, 017172).

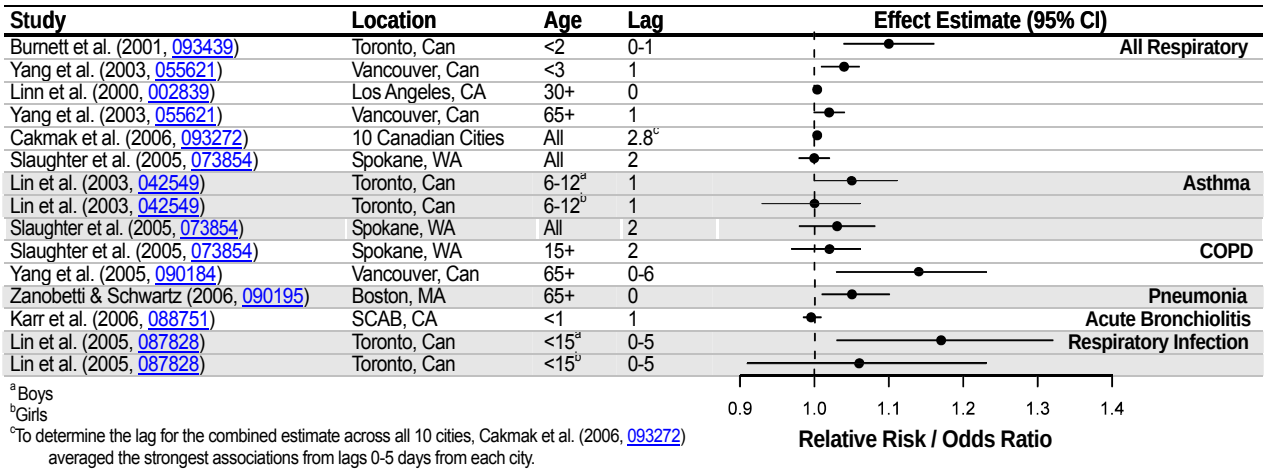


Figure 5-15. Summary of associations for short-term exposure to CO and respiratory hospital admissions.[1,2] Effect estimates were standardized depending on the averaging time used in the study: 0.5 ppm for 24-h avg, 0.75 ppm for max 8-h avg, and 1.0 ppm for 1-h max.

Emergency Department Visits

Respiratory Disease

Peel et al. (2005, 056305) conducted a large single-city respiratory disease ED visit study in Atlanta, GA, which included data from 31 hospitals for the time period 1993–2000. In this study, results were reported for various respiratory-related visits (ICD-9 460-466, 477, 480-486, 491-493, 496, 786.09). In an all-ages analysis, the authors found a RR=1.01 (95% CI: 1.00-1.02) for all respiratory disease ED visits for a 3-day avg (lag 0-2) per 1 ppm increase in 1-h max CO concentration. Tolbert et al. (2007, 090316) expanded the time period used in the Peel et al. (2005, 056305) study to include ED visits through 2004 and reported similar results for all respiratory disease ED visits (RR=1.013 [95% CI: 1.007-1.018] per 1 ppm increase in 1-h max CO). The CO risk estimates from the Atlanta, GA, ED visits studies were attenuated when O_3, NO_2, or PM were added to the model (results not presented quantitatively), which could potentially be explained by the high correlations reported in Tolbert et al. (2007, 090316) between CO and NO_2 (r = 0.70) and EC (r = 0.66) and the moderate correlation with $PM_{2.5}$ (r = 0.51). One additional ED-visits study that also examined respiratory disease (Slaughter et al., 2005, 073854) presented essentially null results at lag 1 and 2 but found similar results to Peel et al. (2005, 056305) and Tolbert et al. (2007, 090316) at lag 3 (RR=1.02 [95% CI: 1.00-1.03] per 0.5 ppm increase in 24-h avg CO). Slaughter et al. (2005, 073854) reported a weak to moderate correlation between CO and various PM size fractions but did not report the correlation between CO and gaseous pollutants, limiting the comparison of this study with Peel et al. (2005, 056305) and Tolbert et al. (2007, 090316).

Asthma

The association between short-term exposure to CO and asthma ED visits (ICD-9 493, 786.09) was also examined in Atlanta, GA, by Peel et al. (2005, 056305). In this study, the authors reported

[1] Risk estimates from Moolgavkar (2003, 042864) were not included in this figure because the study presented a range of effect estimates using different statistical models. The results from this study were more adequately highlighted in the evaluation of the study in the COPD section.

[2] Risk estimates from Lin et al. (2004, 055600) were not included in the figure because the results were stratified by SES and therefore could not be readily compared to effect estimates from Lin et al. (2003, 042549).

results from distributed lag models including lags 0-13 in addition to a ma of lags 0, 1, and 2 (lag 0-2) for specific respiratory outcomes (e.g., asthma). Effect estimates from the distributed lag models were stronger than those produced from models that used 3-day ma CO concentrations (RR = 1.01 [95% CI: 0.99-1.02] for lags 0-2 compared to RR=1.08 [95% CI: 1.05-1.11] for an unconstrained distributed lag of 0-13 for a 1 ppm increase in 1-h max CO). These results demonstrated the potential effect of CO exposures up to 13 days prior to an asthma ED visit. Estimates were stronger for pediatric ED visits (ages 2-18 yr) (RR=1.02 [95% CI: 1.00-1.04] per 1 ppm increase in 1-h max CO) for a 3-day avg (lag 0-2) compared to all ages (Peel et al., 2005, 056305). Slaughter et al. (2005, 073854), which also examined ED visits for Spokane (1995-2001), reported an increase in asthma ED visits for all ages for CO at lag 3 (RR=1.03 [95% CI: 1.00-1.05] per 0.5 ppm increase in 24-h avg CO) but not for the other two lags examined (lags 1 and 2). The results from Ito et al. (2007, 156594) also provide evidence of increased ED visits for asthma (ICD-9 493) for all ages in New York City for 1999-2002. Using three different models that adjusted for weather variables via different degrees of smoothing and/or a different number of weather variables, the authors found that CO effect estimates remained elevated in both an all-year analysis and in analyses stratified by warm (i.e., April to August) and cold (i.e., November to March) months. Using Model C, which adjusted for temporal trends using 8 degrees of freedom (df) and included variables to adjust for weather and day of the week, an all-year RR of 1.03 (95% CI: 1.01-1.06) per 0.75 ppm increase in maximum 8-h avg CO concentrations was reported. Ito et al. (2007, 156594) also examined copollutant models using Model C but only during the warm season. In this model CO effect estimates were robust to the inclusion of $PM_{2.5}$ (RR = 1.06 [95% CI: 1.00-1.11]), O_3 (RR=1.10 [95% CI: 1.05-1.15]), and SO_2 (RR=1.04 [95% CI: 0.99, 1.09]) in the model, but the CO risk estimate was attenuated, resulting in a negative effect estimate when including NO_2 (RR=0.97 [95% CI: 0.92-1.03]) in the model.

Chronic Obstructive Pulmonary Disease

In the examination of the effect of short-term exposure to CO on COPD ED visits (ICD-9 491, 492, 496), Peel et al. (2005, 056305) reported elevated estimates for Atlanta, GA, for 1993-2000 (RR=1.03 [95% CI: 1.00-1.05] per 1 ppm increase in 1-h max CO for lag 0-2 ma) with similar results for the distributed lag model (RR=1.03 [95% CI: 0.98-1.09). However, results from Slaughter et al. (2005, 073854) from Spokane, WA, were consistent with a null or slightly protective association at lag 1 (RR=0.96 [95% CI: 0.92-1.00] per 0.5 ppm increase in 24-h avg CO at lag 1) with similar results for lags 2 and 3.

Pneumonia and Other Respiratory Infections

Similar to the HA analysis conducted by Zanobetti and Schwartz (2006, 090195) discussed above, Peel et al. (2005, 056305) examined the effect of CO on pneumonia separately (ICD-9: 480-486) but also included an analysis of upper respiratory infection (ICD-9: 460-466, 477) ED visits for all ages in Atlanta, GA, during the years 1993-2000. The authors reported a weak estimate for pneumonia for the 3-day ma (lag 0-2) (RR=1.01 [95% CI: 0.996-1.021] per 1 ppm increase in 1-h max CO). However, when using an unconstrained distributed lag model (days 0-13), Peel et al. (2005, 056305) observed evidence of an association (RR=1.045 [95% CI: 1.01-1.08]). An examination of upper respiratory infection (URI) ED visits, the largest of the respiratory ED groups, found slightly increased risk estimates for both the 3-day ma (lag 0-2) (RR=1.01 [95% CI: 1.00-1.02]) and the unconstrained distributed lag for days 0-13 (RR=1.07 [95% CI: 1.05-1.09]) per 1 ppm increase in 1-h max CO. In copollutant models, CO risk estimates were largely attenuated when PM_{10}, O_3, or NO_2 were included in the model (not reported quantitatively). Upon conducting an age-stratified analysis, Peel et al. (2005, 056305) also found that infant (<1 yr of age) and pediatric (ages 2-18 yr) URI ED visit CO risk estimates were substantially stronger than the all-age risk estimates.

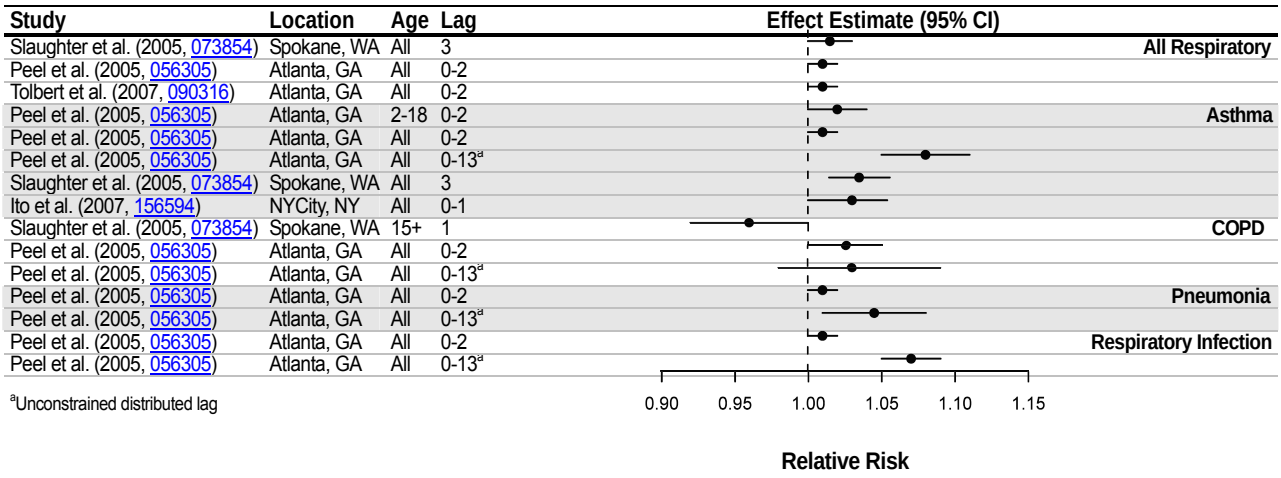


Figure 5-16. Summary of associations for short-term exposure to CO and respiratory ED visits. Effect estimates were standardized depending on the averaging time used in the study: 0.5 ppm for 24-h avg, 0.75 ppm for max 8-h avg, and 1.0 ppm for 1-h max.

Physician Visits

Although HAs and ED visits are the two most well-studied measures of morbidity, a few studies also examined the effect of CO on unscheduled physician visits. In a time-series study, Villeneuve et al. (2006, 091179) examined the effect of CO on physician visits for allergic rhinitis in individuals 65 yr and older in Toronto, Canada. Although quantitative results were only presented in figures, upon observation it was evident that estimates were consistent with a null association for lags 0-6 (Villeneuve et al., 2006, 091179). In an additional study, Sinclair et al. (2004, 088696) reported results for urgent care visits for asthma and respiratory infections in a health maintenance organization in Atlanta, GA; however, the study only reported statistically significant results, of which none were for CO.

Summary of Associations between Short-Term Exposure to CO and Respiratory Hospital Admissions, ED Visits, and Physicians Visits

Compared to other criteria air pollutants (e.g., O_3 and PM), relatively few studies evaluated the association between short-term exposure to ambient CO and HAs and ED visits for various respiratory outcomes. Although evidence for consistent positive associations (Figure 5-15 and Figure 5-16) has been found across the studies evaluated, there remains uncertainty as to a biologically plausible mechanism which could explain the association between CO exposure and respiratory-related health effects. As observed in the preceding section, several authors suggest that the observed associations are due to CO acting as an indicator of combustion-related pollution (e.g., traffic). The interpretation of the associations observed in the studies evaluated is further complicated by the moderate to high correlations reported between CO and other traffic-related pollutants such as NO_2, $PM_{2.5}$, EC, or BC. Only a few studies examined potential confounding of CO risk estimates by copollutants, and these studies found that CO risk estimates were generally robust to the inclusion of O_3, SO_2, and PM in two-pollutant models. However, those studies that examined two-pollutant models with NO_2 found that CO risk estimates, although positive, were slightly attenuated.

5.5.2. Epidemiologic Studies with Long-Term Exposure

The 2000 CO AQCD (U.S. EPA, 2000, 000907) did not evaluate any studies that examined the effect of long-term exposure to CO on respiratory health. The following section discusses those studies that analyze the effect of long-term exposure to CO on pulmonary function, asthma/asthma symptoms, and allergic rhinitis. Table 5-21 lists the studies evaluated in this section along with the respiratory health outcomes examined and CO concentrations reported.

Table 5-21. Range of CO concentrations reported in key respiratory morbidity studies that examined effects associated with long-term exposure to CO.

Study[a]	Location (Sample Size)	Year(s)	Health Outcome	Metric	Mean Concentration (ppm)	Middle/Upper Percentile Concentrations (ppm)
Mortimer et al. (2008, 122163)	San Joaquin Valley, CA (n=232)	1989-2000	Pulmonary function	Monthly mean of max 8-h avg	NR	NR
Meng et al. (2007, 093275)	Los Angeles and San Diego counties, CA	11/2000-9/2001	Asthma symptoms	Annual mean of 1-h avg	NR	NR
Wilhelm et al. (2008, 191912)	Los Angeles and San Diego Counties, CA (n=612)	1999-2001	Asthma symptoms	Annual mean of 1-h avg	1.0	Maximum: 1.8
Goss et al. (2004, 055624)	U.S.	2000	Pulmonary function; Asthma symptoms	Annual mean of 1-h avg	0.69	25th: 0.48 50th: 0.59 75th: 0.83
Hirsch et al. (1999, 003537)	Dresden, Germany	9/1995-6/1996	Respiratory symptoms	Annual mean of 0.5-h avg	0.60	75th: 0.76 Maximum: 1.34
Guo et al. (1999, 010937)	Taiwan	1994	Asthma; Asthma symptoms	Annual mean of monthly avg	0.85	50th: 0.84 75th: 1.00 Maximum: 1.61
Wang et al. (1999, 008105)	Kaohsiung and Pintong, Taiwan	1996	Asthma	Annual avg	NR	50th: 0.80
Hwang et al. (2005, 089454)	Taiwan	2000	Asthma	Annual mean of monthly avg	0.66	50th: 0.65 75th: 0.75 Maximum: 0.96
Hwang et al. (2006, 088971)	Taiwan	2000	Allergic rhinitis	Annual mean of monthly avg	0.66	50th: 0.65 75th: 0.75 Maximum: 0.96
Lee et al. (2003, 049201)	Taiwan	1994	Allergic rhinitis	Annual avg	0.85	50th: 0.84 75th: 1.00 Maximum: 1.61
Arnedo-Pena et al. (2009, 190238)	7 Spanish cities	2000	Asthma, allergic rhinitis, atopic eczema	Annual avg		50th: 0.61 75th: 0.78 Maximum: 1.04
Mortimer et al. (2008, 187280)	Fresno, CA (n=170)	11/2000-4/2005	Allergic sensitization	Monthly mean of 24-h avg	NR[b]	NR[b]

[a]The number of individuals included in the study population was only provided for those studies that included less than 1,000 participants.
[b]This study only presented air quality data graphically.

5.5.2.1. Pulmonary Function

Mortimer et al. (2008, 122163) examined the effect of prenatal and lifetime exposures to air pollutants on pulmonary function in 232 asthmatic children who resided in the San Joaquin Valley of California. The strong temporal correlation between pollutants and pollutant metrics for different time periods in the study area contributed to the inability to draw conclusions about the effect of

individual pollutant metrics on pulmonary function (Mortimer et al., 2008, 122163). The authors used a newly developed Deletion/Substitution/Addition (DSA) algorithm "to identify which pollutant metrics were most predictive of pulmonary function" (Mortimer et al., 2008, 122163). This methodology uses an exploratory process to identify the best predictive model for each outcome of interest. Focusing specifically on the exposure durations after birth, using this approach, Mortimer et al. (2008, 122163) found that exposure to CO early in life, ages 0-3 yr, was negatively associated with FEV_1/FVC, resulting in an effect size of -2.5% per IQR increase in CO.[1] Additional negative associations were observed between exposure to CO during the first 6 yr of life and FEF_{25} (-6.7%) and FEF_{25-75}/FVC (-4.8%) in children diagnosed with asthma prior to 2 yr of age. Overall, Mortimer et al. (2008, 122163) found that these effects were limited to subgroups, including African-Americans and individuals diagnosed with asthma before the age of 2 yr. It must be noted that research still needs to be conducted to validate the aforementioned results obtained using the DSA algorithm and the subsequent calculation of effect estimates using GEE because the current model could underestimate the uncertainty surrounding the associations reported (Mortimer et al., 2008, 122163). Although the authors did find associations between long-term exposure to CO and decrements in pulmonary function, they also observed high correlations between CO and NO_2, which together are markers for pollutants generated by urban combustion sources (e.g., mobile sources) (Mortimer et al., 2008, 122163).

Goss et al. (2004, 055624) also examined the effect of long-term exposure to CO on pulmonary function in a cohort of cystic fibrosis patients >6 yr of age enrolled in the Cystic Fibrosis National Patient Registry in 1999 and 2000. When examined cross-sectionally in 2000 using a multiple linear regression model, the authors found no association between CO and a reduction in FEV_1. However, Goss et al. (2004, 055624) recognize that the CO results could be influenced by measurement error and subsequently exposure misclassification.

5.5.2.2. Asthma and Asthma Symptoms

U.S.-based studies consistently reported no association between long-term exposure to CO and asthma and asthma symptoms. Wilhelm et al. (2008, 191912) and Meng et al. (2007, 093275) both examined the association between long-term exposure to air pollutants and asthma symptoms in respondents to the 2001 California Health Interview Survey (CHIS) in populations consisting of children (0-17 yr) and adults (≥ 18 yr), respectively, who resided in Los Angeles and San Diego counties. Using a cross-sectional study design, Meng et al. (2007, 093275) found no association between long-term exposure to CO and poorly controlled asthma in adults, while Wilhelm et al. (2008, 191912) reported no associations between long-term exposure CO and asthma symptoms or asthma HA and ED visits in children during the study period (i.e., 2000-2001). In an additional U.S.-based study, Goss et al. (2004, 055624) found no association (OR=1.01 [95% CI: 0.92-1.10] per 0.5 ppm increase in annual average CO concentrations) between long-term exposure to CO and pulmonary exacerbations in a national cohort of individuals with cystic fibrosis >6 yr of age.

Among studies conducted in other countries, a study conducted in Germany (Hirsch et al., 1999, 003537) and studies conducted in Taiwan (Guo et al., 1999, 010937; Hwang et al., 2005, 089454; Wang et al., 1999, 008105), all found positive associations between long-term exposure to CO and asthma or asthma symptoms in populations ranging from 6 to 16 yr old. In these studies, the authors addressed the observed associations differently. Guo et al. (1999, 010937) and Hwang et al. (2005, 089454) both concluded that it is unlikely CO directly affects the respiratory system; Hirsch et al. (1999, 003537) attributed the increase in the prevalence of cough and bronchitis to exposure to traffic-related air pollutants (i.e., NO_2, CO, and benzene); and Wang et al. (1999, 008105) did not interpret the association observed between long-term exposure to CO and adolescent asthma. Only Hwang et al. (2005, 089454) conducted a copollutant analysis and found that the asthma effects observed were robust to the inclusion of PM_{10}, SO_2 and O_3 in the model. However, this study did not include NO_X in a copollutant model, which is notable because NO_X was found to be highly correlated with CO (r = 0.88).

[1] The study did not present the IQR for CO; therefore, the effect estimates presented were not standardized using the approach mentioned previously in this ISA.

5.5.2.3. Respiratory Allergy and Other Allergic Responses

Allergy is a major contributor to asthma and upper respiratory symptoms; as a result, studies have examined the effect of air pollutants on allergic outcomes. The studies evaluated that examined the association between long-term exposure to CO and allergic outcomes were primarily conducted outside of the U.S. and Canada. A multicity study conducted in 7 Spanish cities found that the annual average concentration of CO was associated with a higher prevalence of allergic rhinitis, rhinoconjunctivitis, and atopic eczema in 6- to 7-yr-old children (Arnedo-Pena et al., 2009, 190238). NO_2 was also examined and found to be positively associated with allergic rhinitis, but, unlike CO, was negatively associated with eczema and rhinoconjunctivitis. It should be noted that in this data set CO and NO_2 concentrations were negatively correlated ($r = -0.55$). Additionally, SO_2 was positively associated with all allergic outcomes, while TSP matter was inversely associated with rhinitis and rhinoconjunctivitis. Hwang et al. (2006, 088971) and Lee et al. (2003, 049201) both examined the effect of long-term exposure to air pollutants on the prevalence of allergic rhinitis in a population of schoolchildren in Taiwan. Both studies found an association between allergic rhinitis prevalence and CO, but they also observed an association with NO_X. As a result, although Hwang et al. (2006, 088971) and Lee et al. (2003, 049201) observed an increase in the prevalence of allergic rhinitis in response to an increase in long-term CO levels, they concluded that the combination of an association being observed for both CO and NO_X can be attributed to the complex mixture of traffic-related pollutants and not necessarily CO alone. Although questions surround the associations observed between long-term exposure to CO and allergic outcomes, the results are consistent with those presented in a multicity study that examined the association between short-term exposure to CO and allergic symptoms. Moon et al. (2009, 190297) observed associations between short-term CO exposure and allergic symptoms in children in South Korea. However, allergic symptoms were also associated with other pollutants, including PM_{10}, SO_2, and NO_2, and the study did not present correlation coefficients to allow for further analysis of the results. It should be noted that toxicological experiments suggest that endogenously produced CO may play an integral part in the pathogenesis of allergic rhinitis, resulting in an additional potential pathway for CO-induced allergic outcomes (Shaoqing et al., 2008, 192384).

Allergic symptoms such as rhinitis are a direct result of allergic sensitization, which is commonly measured by skin prick testing or IgE antibody measurement. Hirsch et al. (1999, 003537), in a single-city study conducted in Dresden, Germany, observed no associations between annual average concentrations of CO, NO_2, SO_2, or O_3 and allergy assessed by skin prick testing or serum IgE measurement in schoolchildren. However, prenatal exposure to CO was associated with allergic sensitization in a cohort of 6- to 11-year-old asthmatic children in California (Mortimer et al., 2008, 187280). Skin prick tests indicated higher levels of sensitization to indoor and outdoor allergens with an increase in CO exposure during the prenatal period; the association with sensitization to outdoor allergens remained after adjustment for effect modifiers, copollutants, and other potential confounders. Mortimer et al. (2008, 187280) also found that PM_{10} exposure was associated with sensitization to indoor allergens but was not significant after adjustment. Additionally, despite strong correlations between CO and NO_2, no associations were reported with NO_2. It should be noted that these results were produced using the DSA algorithm and, as discussed previously, additional research is still needed to evaluate the use of this method in air pollution epidemiology (Mortimer et al., 2008, 122163).

5.5.2.4. Summary of Associations between Long-Term Exposure to CO and Respiratory Morbidity

To date, a limited number of studies have examined the potential association between long-term exposure to CO and respiratory morbidity. Although studies have reported positive associations for various respiratory outcomes, the limited evidence available, the new analytical methods employed, and the lack of studies that examined potential confounders of the CO-respiratory morbidity relationship, especially due to the high correlation between CO and other traffic-related pollutants, makes it difficult to attribute the associations observed to CO independent of other air pollutants.

5.5.3. Controlled Human Exposure Studies

Human clinical studies provide very little and inconsistent evidence of changes in pulmonary function following exposure to CO. In one older study, Chevalier et al. (1966, 010641) observed a significant decrease in total lung capacity following a short-term exposure to 5,000 ppm resulting in a COHb level of 4%. However, a similar study conducted at a higher CO concentration resulting in COHb levels of 17-19% found no CO-induced changes in lung volume or mechanics (Fisher et al., 1969, 012381). The 2000 CO AQCD (U.S. EPA, 2000, 000907) reported no evidence of CO-induced changes in exercise ventilation at COHb levels <15% during submaximal exercise (Koike et al., 1991, 013500). In two recent human clinical studies, exposure to CO (COHb ≈ 10%) was not found to significantly affect resting pulmonary ventilation compared with exposure to clean air under either hypoxic or hyperoxic exposure conditions (Ren et al., 2001, 193850; Vesely et al., 2004, 194000). The results of these studies demonstrate that the hypoxia- and CO_2-induced increases in pulmonary ventilation are not affected by CO. One recent study evaluated the potential anti-inflammatory effects of controlled exposures to CO in the airways of 19 individuals with COPD (Bathoorn et al., 2007, 193963). Subjects were exposed to both CO at concentrations of 100-125 ppm as well as room air for 2 h on each of 4 consecutive days. The authors reported a small decrease in sputum eosinophils, as well as a slight increase in the provocative concentration of methacholine required to cause a 20% reduction in FEV_1 following exposure to CO. Although this study appears to demonstrate some evidence of an anti-inflammatory effect of CO among subjects with COPD, it must be noted that two of these patients experienced exacerbations of COPD during or following CO exposure. A similar study found no evidence of systemic anti-inflammatory effects following exposure to higher CO concentrations (500 ppm for 1 h) in a group of healthy adults (Mayr et al., 2005, 193984).

5.5.4. Toxicological Studies

As discussed in Section 5.2.5, the work of Thom, Ischiropoulos and colleagues (Ischiropoulos et al., 1996, 079491; Thom and Ischiropoulos, 1997, 085644; Thom et al., 1997, 084337; Thom et al., 1999, 016753; Thom et al., 1999, 016757) focused on CO-mediated displacement of NO from heme-binding sites. Although the concentrations of CO used in many of their studies were far higher than ambient levels, some of this research involved more environmentally-relevant CO levels. In one study (Thom et al., 1999, 016757), 1-h exposure of rats to 50 ppm CO resulted in increased lung capillary leakage 18 h later. Increased NO was observed in the lungs by electron paramagnetic resonance during 1-h exposure to 100 ppm CO and was accompanied by increases in H_2O_2 and nitrotyrosine. All of these effects were blocked by inhibition of NOS. These results, which were partially discussed in the 2000 CO AQCD (U.S. EPA, 2000, 000907), demonstrate the potential for exogenous CO to interact with NO-mediated pathways and to lead to pathophysiological effects in the lung.

Recent work by Ghio et al. (2008, 096321) showed a disruption of cellular iron homeostasis following exposure to a low level of CO (50 ppm for 24 h) in rats. In lungs of inhalation-exposed rats, non-heme iron was significantly reduced, while lavagable iron was increased dramatically, suggesting an active removal of cellular iron. Lavagable ferritin was also increased following the CO exposure. Concurrently, liver iron levels increased, implying that the anatomical distribution of iron stores may significantly shift during/after CO exposures. These investigators were able to replicate the effect of loss of cellular iron in an in vitro model of cultured BEAS-2B cells and reported statistically significant effects at 10 ppm CO and an apparent maximal effect at 50 ppm CO (concentrations up to 500 ppm did not significantly enhance the iron loss beyond 50 ppm). Similar responses were observed for cellular ferritin. Both enhancement of iron removal and diminished iron uptake were noted in CO-exposed cells. Furthermore, decreased oxidative stress, mediator release and proliferation were noted in respiratory cells. These effects were reversible with a recovery period in fresh air. Interestingly, the in vivo exposure to CO induced mild but significant neutrophilia in the lungs compared to air-exposed rats. This finding is contrary to the concept that CO acts as an anti-inflammatory agent; however, with alterations in iron handling several potential pathways could be initiated to recruit inflammatory cells into airways. The authors pointed out that while CO derived from HO activity may have an important role in iron regulation, the nonspecific application of exogenous CO would have little capacity to discriminate between excessive and/or inappropriate iron which catalyzes oxidative stress and iron which may be required for normal homeostasis.

A chronic inhalation study by Sorhaug et al. (2006, 180414) demonstrated no alterations in lung morphology in Wistar rats exposed to 200 ppm CO for 72 wk. COHb levels were reported to be 14.7%, and morphological changes were noted in the heart as described in Section 5.2.5.2.

A recent study by Carraway et al. (2002, 026018) involved continuous exposure of rats to HH (380 torr) with or without co-exposure to CO (50 ppm) for up to 21 days. The focus of this study was on remodeling of the pulmonary vasculature. While the addition of CO to HH did not alter the thickness or diameter of vessels in the lung, there was a significant increase in the number of small (<50 μm) diameter vessels compared to control, HH-only, and CO-only exposures. Despite the greater number of vessels, the overall pulmonary vascular resistance was increased in the combined CO + HH exposure, which the authors attribute to enhancement of muscular arterioles and β-actin.

One new study found an association between increased endogenous CO and the development of allergic rhinitis (Shaoqing et al., 2008, 192384). In this model, guinea pigs which were sensitized and challenged with ovalbumin exhibited high immunoreactivity of HO-1 in the nasal mucosa and a more than doubling of blood COHb levels (measured by gas chromatography). It is not known whether the observed increase in endogenous CO resulting from ovalbumin-mediated inflammation/oxidative stress plays a role in the development of allergic rhinitis but suggests a potential mechanism by which exogenous CO could impact an allergic phenotype.

In summary, one older study (Thom et al., 1999, 016757) and two new studies (Carraway et al., 2002, 026018; Ghio et al., 2008, 096321) demonstrated effects of 50-100 ppm CO on the lung. Responses included an increase in alveolar capillary permeability, disrupted iron homeostasis, mild pulmonary inflammation, and an exacerbation of pulmonary vascular remodeling elicited by HH. These results should be considered in view of the potential for inhaled CO to interact directly with lung epithelial cells and resident macrophages. However, a chronic study involving 200 ppm CO demonstrated no changes in pulmonary morphology (Sorhaug et al., 2006, 180414).

5.5.5. Summary of Respiratory Health Effects

5.5.5.1. Short-Term Exposure to CO

New epidemiologic studies, supported by the body of literature summarized in the 2000 CO AQCD (U.S. EPA, 2000, 000907), provide evidence of positive associations between short-term exposure to CO and respiratory-related outcomes including pulmonary function, respiratory symptoms, medication use, HAs, and ED visits. The majority of the studies evaluated did not conduct extensive analyses to examine the potential influence of model selection or effect modifiers on the association between CO and respiratory morbidity. A limited number of studies examined the potential confounding effects of copollutants on CO risk estimates and found that CO risk estimates were generally robust to the inclusion of O_3, SO_2, and PM in two-pollutant models but were slightly attenuated in models with NO_2. However, the limited amount of evidence from studies that examined the effect of gaseous pollutants on CO-respiratory morbidity risk estimates in two-pollutant models, specifically NO_2, has contributed to the inability to disentangle the effects attributed to CO from the larger complex air pollution mix (particularly motor vehicle emissions), and this limits interpretation of the results observed in the epidemiologic studies evaluated. A key uncertainty in interpreting the epidemiologic studies evaluated is the biological mechanism(s) that could explain the effect of CO on respiratory health. Animal toxicological studies, however, provide some evidence that short-term exposure to CO (50-100 ppm) can cause oxidative injury and inflammation and alter pulmonary vascular remodeling. Controlled human exposure studies have not extensively examined the effect of short-term exposure to CO on respiratory morbidity, with a very limited number of studies reporting inconsistent effects of CO on pulmonary function. Although these controlled human exposure studies do not provide evidence to support CO-related respiratory health effects, epidemiologic studies show positive associations for CO-induced lung-related outcomes and animal toxicological studies demonstrate the potential for an underlying biological mechanism, which together provide evidence that is **suggestive of a causal relationship between relevant short-term exposures to CO and respiratory morbidity.**

5.5.5.2. Long-Term Exposure to CO

Currently, only a few studies have been conducted that examine the association between long-term exposure to CO and respiratory morbidity including allergy. Although some studies did observe associations between long-term exposure to CO and respiratory health outcomes, key uncertainties still exist. These uncertainties include: the lack of replication and validation studies to evaluate new methodologies (i.e., Deletion/Substitution/Addition (DSA) algorithm) that have been used to examine the association between long-term exposure to CO and respiratory health effects; whether the respiratory health effects observed in response to long-term exposure to CO can be explained by the proposed biological mechanisms; and the lack of copollutant analyses to disentangle the respiratory effects associated with CO due to its high correlation with NO_2 and other combustion-related pollutants. Overall, the evidence available is **inadequate to conclude that a causal relationship exists between relevant long-term exposures to CO and respiratory morbidity.**

5.6. Mortality

5.6.1. Epidemiologic Studies with Short-Term Exposure to CO

Epidemiologic studies have traditionally focused on mortality effects associated with exposure to PM and O_3, resulting in a limited number of studies that have conducted extended analysis to examine the potential influence of model selection, effect modifiers, or confounders on the association between CO and mortality. This has contributed to the inability to formulate a clear understanding of the association between short-term exposure to CO and mortality. This section summarizes the main findings of the 2000 CO AQCD (U.S. EPA, 2000, 000907) and evaluates the newly available information on the relationship between short-term exposure to CO and daily mortality in an effort to disentangle the CO-mortality effect from those effects attributed to other criteria air pollutants.

5.6.1.1. Summary of Findings from 2000 CO AQCD

The 2000 CO AQCD (U.S. EPA, 2000, 000907) examined the association between short-term exposure to CO and mortality through the analysis of primarily single-city time-series studies, with additional evidence from one multicity study which included 11 Canadian cities. While the results presented by these studies did provide suggestive evidence that an association exists between CO and mortality, the AQCD concluded that inadequate evidence existed to infer a causal association between mortality and short-term exposure to ambient concentrations of CO. Multiple uncertainties were identified in the epidemiologic literature that contributed to this conclusion, which were discussed in Section 5.2.1.

The majority of the recent time-series mortality studies, as mentioned previously, have not extensively examined the CO-mortality relationship. As such, CO has usually been considered as one of the potential confounding copollutants in air pollution epidemiologic studies. Given the limitation that most of these studies were not conducted to examine CO, the goal of this review is to evaluate the CO-mortality association and specifically the consistency of associations across studies, along with evidence of confounding and effect modification.

5.6.1.2. Multicity Studies

The following sections evaluate the recent literature that examined the association between short-term exposure to CO and mortality, and, in addition, discuss newly available information with regard to the issues specific to CO mentioned above. This evaluation focuses primarily on multicity studies because they provide a more representative sample of potential CO-related mortality effects and especially useful information by analyzing data from multiple cities using a consistent method,

and thus avoiding potential publication bias.[1] Table 5-22 details the multicity studies evaluated along with the mean CO concentrations reported in each study.

Table 5-22. Range of CO concentrations reported in multicity studies that examine mortality effects associated with short-term exposure to CO.

Study	Location	Years	Averaging Time	Mean Concentration (ppm)	Range of Mean Concentrations Across Cities (ppm)
Dominici et al. (2003, 056116; 2005, 087912); Reanalysis of Samet et al. (2000, 156939)	82 US cities[a] (NMMAPS)	1987-1994	24-h avg	1.02	Baton Rouge = 0.43 Spokane = 2.19
Burnett et al. (2004, 086247)	12 Canadian cities	1981-1999	24-h avg	1.02	Winnipeg = 0.58 Toronto = 1.31
Samoli et al. (2007, 098420)[b]	19 European cities (APHEA2)	1990-1997[c]	8-h max	2.12	Basel = 0.52 Athens = 5.3

[a]The study actually consisted of 90 U.S. cities, but only 82 had CO data.
[b]This study presented CO concentrations in the units mg/m^3. The concentrations were converted to ppm using the conversion factor 1 ppm = 1.15 mg/m^3, which assumes standard atmosphere and temperature.
[c]The study period varied from city to city. These years represent the total years in which data was collected across all cities.

National Morbidity, Mortality, and Air Pollution Study of 90 U.S. Cities

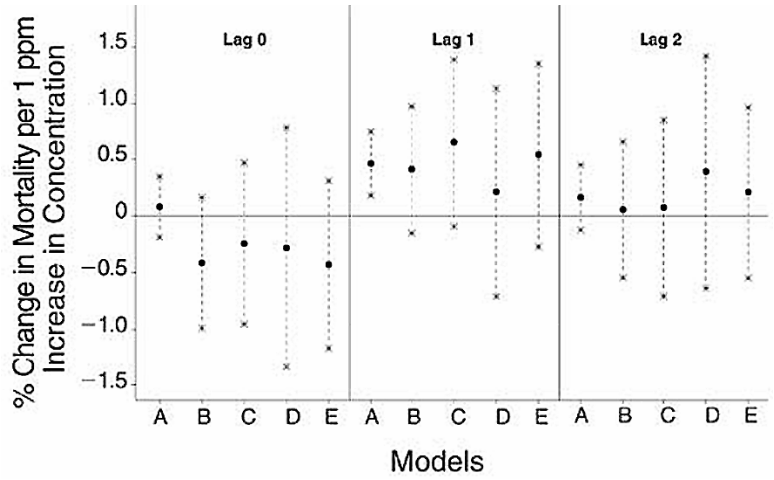
The time-series analysis of the 90 largest U.S. cities (82 cities for CO) in the National Morbidity, Mortality, and Air Pollution Study (NMMAPS) (Dominici et al., 2003, 056116; Dominici et al., 2005, 087912; a reanalysis of Samet et al., 2000, 156939) is by far the largest multicity study conducted to date to investigate the mortality effects of air pollution; however, the study primarily focused on PM_{10}. The range in 24-h avg CO concentrations in a subset of the largest 20 cities (by population size) was 0.66 ppm (Detroit, MI) to 2.04 ppm (New York City). The analysis in the original report used GAM with default convergence criteria. In response to the bias observed in the estimates generated using GAM models with default convergence criteria (Dominici et al., 2002, 030458), Dominici et al. (2003, 056116; 2005, 087912)(reanalysis of Samet et al. (2000, 156939) conducted a reanalysis of the original data using GAM with stringent convergence criteria as well as GLM.

Focusing on the results obtained using GLM, PM_{10} and O_3 (in summer) appeared to be more strongly associated with mortality than the other gaseous pollutants. The authors stated that the results did not indicate associations between CO, SO_2, or NO_2, and total (nonaccidental) mortality. However, as with PM_{10}, the gaseous pollutants CO, SO_2, and NO_2 each showed the strongest association at a 1-day lag (for O_3, a 0-day lag). Figure 5-17 presents the total mortality risk estimates for CO from Dominici et al. (2003, 056116). The authors found a mortality risk estimate of 0.23% (95% PI: 0.09-0.36) per 0.5 ppm increase in 24-h avg CO for a 1-day lag in a single-pollutant model. The inclusion of PM_{10} or PM_{10} and O_3 in the model did not reduce CO risk estimates. However, the confidence intervals were wider in the multipollutant models; however, this could be attributed to: (1) PM_{10} data in many of the cities being collected every 6th day as opposed to daily data for gaseous pollutants; and (2) O_3 being collected in some cities only during warm months. The addition of NO_2 (along with PM_{10}) to the model resulted in a reduced CO risk estimate. Some caution is required when interpreting this apparent reduction because a smaller number of cities (57 cities[2]) were available for the CO multipollutant analysis with PM_{10} and NO_2 compared to the single-pollutant CO analysis (82 cities). However, most of the 32 cities that were excluded due to the lack of NO_2 data were some of the least populated cities. Thus, the difference in the number of cities in the multi- and single-pollutant analyses is unlikely to be the underlying cause for the reduction in the

[1] To compare studies in this section that used different averaging times, effects estimates were standardized to the following: 0.5 ppm for studies that used 24-h avg concentrations and 0.75 ppm for studies that used max 8-h avg concentrations. These standardized values represent the range of current mean ambient concentrations across the U.S.

[2] One city was excluded from the multipollutant analysis because it contained NO_2 data but did not contain CO data.

CO risk estimate in the CO multipollutant analysis with PM_{10} and NO_2. In comparison to the PM_{10} risk estimates which were not reduced in multipollutant models, the CO risk estimates from multipollutant models indicate less consistent associations with mortality.



Source: Reprinted with Permission of HEI from Dominici et al.(2003, 056116)

Figure 5-17. Posterior means and 95% posterior intervals of national average estimates for CO effects on total (nonaccidental) mortality at lags 0, 1, and 2 within sets of the 90 U.S. cities with available pollutant data. Models A = CO alone; B = CO + PM_{10}; C = CO + PM_{10} + O_3; D = CO + PM_{10} + NO_2; E = CO + PM_{10} + SO_2.

Canadian Multicity Studies

Since the 2000 CO AQCD (U.S. EPA, 2000, 000907), two Canadian multicity studies have been published that examined the association between mortality and short-term exposure to air pollutants: (1) an analysis of PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, and gaseous pollutants in 8 cities from 1986 to 1996 (Burnett et al., 2000, 010273); and (2) an analysis of PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, and gaseous pollutants in 12 cities from 1981 to 1999 (Burnett et al., 2004, 086247). The 2000 study (Burnett and Goldberg, 2003, 042798) utilized GAM with default convergence criteria and, upon reanalysis, only examined PM indices.

Burnett et al. (2004, 086247) is the most extensive Canadian multicity study conducted to date, both in terms of the length of the study and the number of cities covered. This study focused primarily on NO_2-mortality associations because it was found to be the best predictor of fluctuations in mortality among the air pollutants examined (NO_2, O_3, SO_2, CO, $PM_{2.5}$, and $PM_{10-2.5}$); however, the study did present single- and copollutant results for all pollutants included in the analysis. The mean CO concentrations reported by Burnett et al. (2004, 086247) are similar to those reported in NMMAPS (Table 5-22).

Burnett et al. (2004, 086247) examined the effect of short-term exposure to CO on total (nonaccidental) mortality. The authors found the strongest mortality association at lag 1-day for CO, SO_2, $PM_{2.5}$, $PM_{10-2.5}$, PM_{10} (arithmetic addition of $PM_{2.5}$ and $PM_{10-2.5}$), and CoH, whereas for NO_2, the strongest association was for the 3-day ma (i.e., average of 0-, 1-, and 2-day lags), and for O_3, it was the 2-day ma. In this study, Burnett et al. (2004, 086247) used 24-h avg pollutant concentrations because these values showed stronger associations with mortality than the daily 1-h max values for all of the gaseous pollutants and CoH but not for O_3. In a single-pollutant model, the CO risk estimate for total (nonaccidental) mortality was 0.33% (95% CI: 0.12-0.54) per 0.5 ppm increase in 24-h avg CO at lag 1. After adjusting for NO_2, the CO risk estimate was reduced to 0.04% (95% CI: -0.19 to 0.26), while the NO_2 risk estimate was only slightly affected (increased from 2.25 to 2.35%) when including CO in the model. In this analysis, a copollutant model including both CO

and PM was not presented. The results presented in this Canadian multicity study and NMMAPS are similar in that the CO risk estimates appeared to be sensitive to the addition of NO_2 in the regression model. However, interpretation of these results requires some caution because: (1) NO_2 tends to have a more spatially uniform distribution within a city compared to CO; (2) CO and NO_2 share common sources (e.g., traffic); and (3) CO and NO_2 are often moderately to highly correlated.

Air Pollution and Health: A European Approach

Most of the Air Pollution and Health: A European Approach (APHEA) analyses have focused on the mortality effects of PM (PM_{10} and BS), SO_2, NO_2, and O_3, but not CO. In addition, some of the analyses have not even considered CO as a potential confounder, such as the extended analysis (APHEA2) of PM (Katsouyanni et al., 2001, 019008) and NO_2. Gryparis et al. (2004, 057276) did consider CO as a potential confounder in an analysis of O_3 and found that the addition of CO increased O_3 mortality risk estimates both in the summer and winter, although the number of cities included in the copollutant model were reduced from 21 to 19. However, the study did not present CO risk estimates. Unlike other APHEA studies (or the NMMAPS and Canadian multicity studies), the Samoli et al. (2007, 098420) analysis focused specifically on CO.

Samoli et al. (2007, 098420) investigated the effect of short-term exposure to CO on total (nonaccidental) and cardiovascular mortality in 19 European cities participating in the APHEA2 project by using a two-stage analysis to examine city-specific effects and potential sources of heterogeneity in CO-mortality risk estimates. The mean levels of the max 8-h avg CO concentration in this study ranged from 0.52 ppm (Basel, Switzerland, and The Netherlands) to 5.3 ppm (Athens, Greece). The max 8-h avg CO concentration across all cities in the APHEA2 study of 2.12 ppm is higher than the estimated max 8-h avg CO concentrations reported for the U.S. cities examined in Dominici et al. (2003, 056116; 2005, 087912) and the Canadian cities examined in Burnett et al. (2004, 086247) of 1.53 ppm.[1] In APHEA cities, the correlation between CO and BS (r = 0.67-0.82) was higher than the correlation between CO and PM_{10} (r = 0.16-0.70) or CO and 1-h max NO_2 (r = 0.03-0.68).

To examine the CO-mortality relationship, Samoli et al. (2007, 098420) conducted a time-series analysis of individual cities following the revised APHEA2 protocol.[2] The primary results presented by the authors are from a sensitivity analysis that used two alternative methods to select the extent of adjustment for temporal confounding. These methods consisted of: (1) confining the extent of smoothing to 8 df/yr; and (2) selecting the appropriate extent of smoothing through minimization of the absolute value of the sum of partial autocorrelation functions (PACF) of the residuals, which resulted in the analysis using on average 5 df/yr for total (nonaccidental) mortality and 4 df/yr for cardiovascular mortality. The authors also conducted copollutant analyses using PM_{10}, BS, SO_2, NO_2, or O_3 (1 h). In the second stage model, Samoli et al. (2007, 098420) examined heterogeneity in CO risk estimates between cities by regressing risk estimates from individual cities on potential effect modifiers including: (1) the air pollution level and mix in each city (i.e., mean levels of pollutants, ratio PM_{10}/NO_2); (2) the exposure (number of CO monitors, correlation between monitors' measurements); (3) variables describing the health status of the population (e.g., crude mortality rate);(4) the geographic area (northern, western, and central-eastern European cities); and (5) climatic conditions (mean temperature and relative humidity levels).

Samoli et al. (2007, 098420) found that CO was associated with total (nonaccidental) and cardiovascular mortality. The primary results represent the combined random effects estimate for a 0.75 ppm increase in max 8-h avg CO concentrations for the average of 0- and 1-day lag for total (nonaccidental) mortality (1.03% [95% CI: 0.55-1.53]) and for cardiovascular mortality (1.08% [95% CI: 0.25-1.90]). These results were obtained using PACF to choose the extent of adjustment for temporal trends. Although the results obtained using PACF are insightful, the use of 8 df/yr would have been more consistent with the NMMAPS model (7 df/yr) and would have allowed for a more accurate comparison of the results between APHEA2 and NMMAPS. The corresponding risk estimates obtained using the 8 df/yr model are 0.57% (95% CI: 0.23-0.91) for total (nonaccidental) mortality and 0.70% (95% CI: 0.31-1.09) for cardiovascular mortality. In the sensitivity analysis,

[1] The max 8-h avg concentration for the Dominici et al. (2003, 056116) and Burnett et al. (2004, 086247) studies was calculated using the conversion factor of 2:3 to convert 24-h avg concentrations to max 8-h avg concentrations.

[2] The APHEA2 protocol used a Poisson GAM model with penalized splines as implemented in the statistical package R.

Samoli et al. (2007, 098420) used 8 or 12 df/yr to adjust for temporal confounding. Both approaches resulted in similar risk estimates, but using PACF to choose the extent of smoothing separately in each city generally resulted in larger CO risk estimates (by ~50-80%). This can be attributed to the smaller number of df/yr used in the model (on average 5 df/yr for total [nonaccidental] mortality and 4 df/yr for cardiovascular mortality), which increases the magnitude of the effect and the amount of observed heterogeneity (Samoli et al., 2007, 098420).

During the examination of the results obtained from the copollutant models, the authors noted that there was indication of confounding of CO risk estimates by BS and NO_2 but not PM_{10}. These results are consistent with CO, BS, and NO_2 being part of the traffic-pollution mixture, and PM_{10} likely including secondary aerosols that do not correlate well with traffic-derived pollution. The risk estimates from the model using 8 df/yr that included NO_2 were 0.26% (-0.09 to 0.61) for total (nonaccidental) mortality and 0.37% (-0.05 to 0.80) for cardiovascular mortality. Thus, the inclusion of NO_2 in the model nearly halved the CO risk estimates (whereas the NO_2 risk estimate was not sensitive to the inclusion of CO in the model). CO risk estimates were reduced by a similar magnitude when including BS in the model. Overall, the sensitivity of CO risk estimates to the inclusion of NO_2 in the model is consistent with the results presented in NMMAPS (Dominici et al., 2003, 056116) and the Canadian multicity study (Burnett et al., 2004, 086247).

In the second-stage model, Samoli et al. (2007, 098420) found that geographic region was the most significant effect modifier, while the other effect modifiers (mentioned above) did not result in strong associations. Effects were primarily found in western and southern European cities and were larger in cities where the standardized mortality rate was lower. Earlier APHEA studies also reported a regional pattern of air pollution associations for BS and SO_2 and found that western cities showed stronger associations than eastern cities. However, the heterogeneity in CO risk estimates by geographic region does not provide specific information to evaluate the CO-mortality association.

An ancillary analysis conducted by Samoli et al. (2007, 098420) examined the possible presence of a CO threshold. The authors compared city-specific models to the threshold model, which consisted of thresholds at 0.5 mg/m^3 (0.43 ppm) increments. Samoli et al. (2007, 098420) then computed the deviance between the two models and summed the deviances for a given threshold over all cities. While the minimum deviance suggested a potential threshold of 0.43 ppm (the lowest threshold examined), the comparison with the linear no-threshold model indicated very weak evidence (p-value >0.9) for a threshold. However, determining the presence of a threshold at the very low range of CO concentrations (i.e., 0.43 ppm) in this data set is challenging because in 7 of the 19 European cities examined, the lowest 10% of the CO distribution was at or above 2 mg/m^3 (1.74 ppm).

In summary, the APHEA2 analysis of CO in 19 cities found an association between CO and total (nonaccidental) and cardiovascular mortality in single-pollutant models, but the associations were substantially reduced when NO_2 or BS was included in copollutant models. The evidence for potential confounding of CO risk estimates by NO_2 is consistent with the findings from NMMAPS and the Canadian 12-city study. In addition, Samoli et al. (2007, 098420) found that geographic region was a potential effect modifier, but such geographic heterogeneity is not specific to CO, based on previously conducted APHEA studies. Finally, examination of the CO concentration-response relationship found very weak evidence of a CO threshold, which requires further investigation.

Other European Multicity Studies

An additional European multicity study was conducted by Biggeri et al. (2005, 087395) in eight Italian cities. The authors examined the effect of short-term exposure to CO on mortality in single-pollutant models using a time-series approach. In this analysis, all of the pollutants showed positive associations with the mortality endpoints examined. However, copollutant models were not examined, and the correlations among the pollutants were not presented; therefore, it is unclear if the observed associations are shared or confounded.

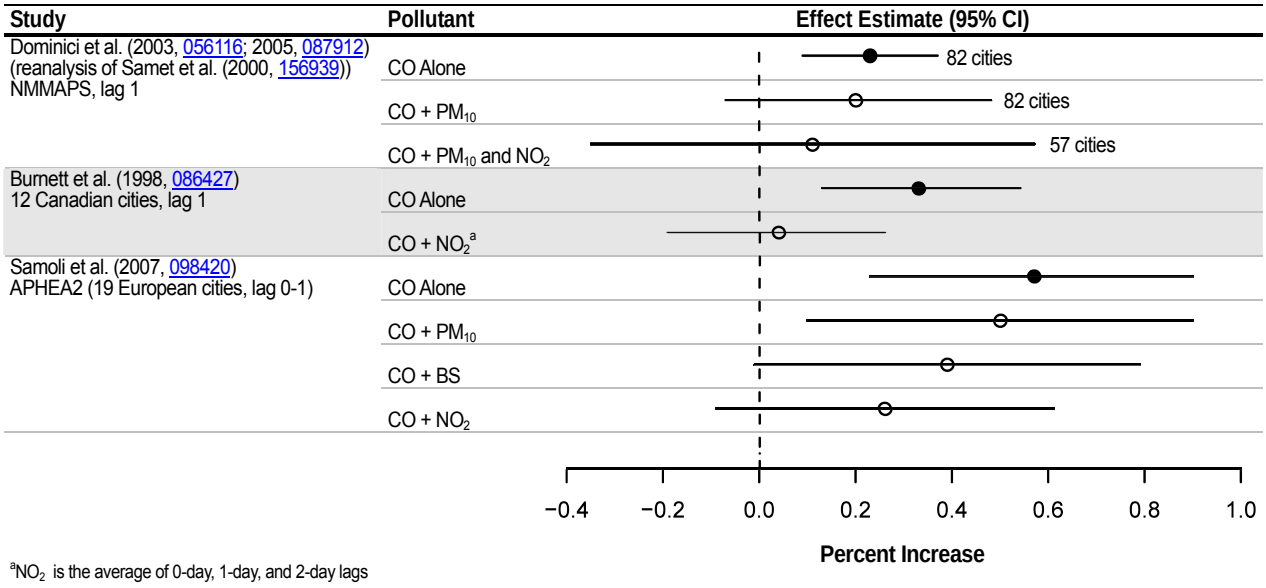
Summary of Multicity Studies

In summary, the mortality risk estimates from single-pollutant models are comparable for the NMMAPS and Canadian 12-city studies, 0.23% and 0.33%, respectively, with the estimate from the

APHEA2 study being slightly larger (0.57%) (Figure 5-18). In both the NMMAPS and Canadian studies, a 1-day lag showed the strongest association; however, the APHEA2 study used an a priori exposure window (i.e., average of 0- and 1-day lags), which has been found to be the exposure window most strongly associated with mortality in PM analyses.

The APHEA2 risk estimates presented in Figure 5-18 are from a model that used a fixed amount of smoothing to adjust for temporal confounding (8 df/yr), which is similar to that used in the NMMAPS study (7 df/yr). However, the APHEA2 sensitivity analysis suggested an approximate 50-80% difference in CO risk estimates between the models that used 8 or 12 df/yr and the models that used minimization of the absolute value of the sum of PACF of the residuals as a criterion to choose the smoothing parameters. Thus, some model uncertainty likely influences the range of CO risk estimates obtained from the studies evaluated.

The CO risk estimates from the aforementioned studies are also consistently sensitive to the inclusion of NO_2 in a copollutant model (0.11, 0.03, and 0.26%, for the NMMAPS, Canadian 12-city study, and APHEA2, respectively). Thus, these results suggest confounding by NO_2. However, this interpretation is further complicated because as with CO, NO_2 itself may be an indicator of combustion sources, such as traffic.



[a]NO_2 is the average of 0-day, 1-day, and 2-day lags

Figure 5-18. Summary of percent increase in total (nonaccidental) mortality for short-term exposure to CO from multicity studies. Estimates were standardized to 0.5 ppm and 0.75 ppm for studies that used 24-h avg CO and max 8-h avg CO exposure metrics, respectively.

5.6.1.3. Meta-Analysis of All Criteria Pollutants

Stieb et al. (2002, 025205) reviewed the time-series mortality studies published between 1985 and 2000 and conducted a meta-analysis to estimate combined effects for PM_{10}, CO, NO_2, O_3, and SO_2. Because many of the studies reviewed in the 2000 analysis used GAM with default convergence criteria, Stieb et al. (2003, 056908) updated the estimates from the meta-analysis by separating the GAM versus non-GAM studies. In this meta-analysis, the authors also presented separate combined estimates for single- and multipollutant models. Overall, there were more GAM estimates than non-GAM estimates for all of the pollutants except SO_2. For CO, 4 single-pollutant model risk estimates were identified, resulting in a combined estimate of 3.18% (95% CI: 0.76-5.66) per 0.5 ppm increase in 24-h avg CO, and only 1 multipollutant model risk estimate (0.00% [95% CI: -1.71 to 1.74]) from the non-GAM studies. Thus, for CO, this study did not provide useful meta-estimates because the number of studies that contributed to the combined estimates for CO was small.

5.6.1.4. Single-City Studies

In addition to the multicity studies discussed above, there have also been several single-city U.S.- and Canadian-based time-series mortality studies that examined CO. The single-city studies, similar to the multicity studies, often focused on the PM-mortality association but also provided additional information that is not available in the multicity studies. Because the sample size used in each single-city study is small and subsequently results in wide confidence intervals, a quantitative comparison of the results from single- and multicity studies is difficult. In addition, some studies do not present CO results quantitatively, adding to the inability to adequately compare studies. Table 5-23 lists the single-city studies evaluated along with the mean CO concentrations reported in each study.

Table 5-23. Range of CO concentrations reported in single-city studies that examine mortality effects associated with short-term exposure to CO.

Study	Location	Years	Averaging Time	Mean Concentration (ppm)	Upper Percentile Concentrations (ppm)
De Leon et al. (2003, 055688)	New York, NY	1985-1994	24-h avg	2.45	95th: 4.04
Klemm et al. (2004, 056585)	Atlanta, GA	1998-2000	1-h max	1.31	Max: 7.40 75th: 1.66
Vedal et al. (2003, 039044)[a]	Vancouver, BC, Can	1994-1996	24-h avg	0.5	Max: 1.9 90th: 0.9
Villeneuve et al. (2003, 055051)	Vancouver, BC, Can	1986-1999	24-h avg	1.0	Max: 4.9 90th: 1.6
Goldberg et al. (2003, 035202)	Montreal, Quebec, Can	1984-1993	24-h avg	0.8	Max: 5.1 75th: 1.0
Hoek et al. (2000, 010350; 2001, 016550); Reanalyzed by Hoek (2003, 042818)	The Netherlands	1986-1994	24-h avg	Entire Country: 0.46 Four Major Cities: 0.59	Max. Entire Country: 2.6 Four Major Cities: 4.6

[a]Study reported median CO concentrations.

Single-City Studies Conducted in the United States

De Leon et al. (2003, 055688) focused on the role of contributing respiratory diseases on the association between air pollution (i.e., PM_{10}, O_3, NO_2, SO_2, and CO) and primary nonrespiratory mortality (circulatory and cancer) in New York City, NY, during the period 1985-1994. This study only presented risk estimates graphically for each of the pollutants analyzed, except PM_{10}. In single-pollutant models, PM_{10}, CO, SO_2, and NO_2 all showed the same pattern of association with circulatory mortality for individuals ≥ 75 yr, indicating a larger risk of death in individuals with contributing respiratory diseases compared to those without. In two-pollutant models, PM_{10} and CO risk estimates were reduced but each remained significantly positive.

Klemm et al. (2004, 056585) analyzed 15 air pollutants for their associations with mortality in Atlanta, GA, for a 2-yr period starting in August 1998. These pollutants included $PM_{2.5}$, $PM_{10-2.5}$, UFP surface area and counts, aerosol acidity, EC, OC, SO_4^{2-}, O_3, CO, SO_2, and NO_2. This study presented risk estimates using three levels of smoothing (quarterly, monthly, and biweekly knots) for temporal trend adjustment and suggested that the risk estimates were rather sensitive to the extent of smoothing. It should be noted that temporal smoothing using biweekly knots is a more aggressive modeling approach than the degrees-of-freedom approach used by most studies. In the single-pollutant models for nonaccidental mortality, the strongest association, which was also statistically significant, was found for $PM_{2.5}$. CO, SO_4^{2-}, and $PM_{10-2.5}$ also showed positive associations with nonaccidental mortality (CO: Quarterly knots and Monthly Knots $\beta = 0.00002$ [SE = 0.00001]; Biweekly knots $\beta = 0.00001$ [SE = 0.00002]). However, CO was significantly associated with circulatory mortality in older adults (≥ 65 yr), and these associations remained when $PM_{2.5}$ was included in the model (results were presented graphically).

Single-City Studies Conducted in Canada

Vedal et al. (2003, 039044) examined the association between short-term exposure to "low levels" of air pollution (i.e., PM_{10}, O_3, NO_2, SO_2, and CO) and daily mortality in Vancouver, British Columbia, Canada, for the years 1994-1996. In this analysis, all of the risk estimates were presented graphically; however, the results suggested that O_3 in the summer and NO_2 in the winter showed the strongest associations with mortality. Vedal et al. (2003, 039044) found that CO was positively but not significantly associated with mortality. Additionally, the association between short-term exposure to NO_2 and mortality was found to be consistent with the results from the Canadian multicity study conducted by Burnett et al. (2004, 086247).

Villeneuve et al. (2003, 055051) also conducted an analysis using data from Vancouver, Canada, using a cohort of 550,000 individuals whose vital status was ascertained between 1986 and 1999. In this study, $PM_{2.5}$, $PM_{10-2.5}$, TSP, CoH, PM_{10}, SO_4^{2-}, O_3, CO, SO_2, and NO_2 were examined for their associations with all-cause (nonaccidental), cardiovascular, and respiratory mortality. When examining the association between gaseous pollutants and all-cause (nonaccidental) mortality in this data set, NO_2 and SO_2 showed the strongest associations, while the association between CO and all-cause mortality were generally weaker than those for NO_2 and SO_2. For cardiovascular mortality, SO_2 risk estimates were smaller than those for NO_2 or CO, while for respiratory mortality, SO_2 showed the strongest associations. However, the wider confidence intervals for these categories and the smaller daily counts make it difficult to assess CO associations with cause-specific mortality outcomes.

Goldberg et al. (2003, 035202) contrasted associations between air pollution and mortality in individuals with underlying CHF versus mortality in individuals who were identified as having CHF 1 yr prior to death based on information from the universal health insurance plan in Montreal, Quebec, Canada, during the period 1984-1993. In this study, Goldberg et al. (2003, 035202) examined associations between $PM_{2.5}$, CoH, SO_4^{2-}, O_3, CO, SO_2, and NO_2, and mortality. The authors found no association between any of the air pollutants and mortality with underlying CHF. However, Goldberg et al. (2003, 035202) found positive associations between air pollution and mortality in individuals diagnosed with CHF 1 yr prior to death. Of the air pollutants examined, CoH, NO_2, and SO_2 were most consistently associated with mortality for ages 65 yr and older, while CO showed positive but weaker associations compared to these three pollutants.

Single-City Studies Conducted in Other Countries

Of the epidemiologic studies conducted in other countries that examine the association between short-term exposure to CO and mortality, only those studies conducted in European countries that have CO levels comparable to the U.S. were evaluated. However, because Samoli et al. (2007, 098420) conducted a multicity study of European cities that focused on short-term exposure to CO, there are only a few single-city studies that provide additional information, specifically those studies conducted in The Netherlands. The Netherland studies were evaluated because they provide risk estimates for multiple pollutants and cause-specific mortality and consisted of relatively large sample sizes (i.e., the mortality time-series of the entire country was analyzed).

Hoek et al. (2000, 010350) (reanalyzed by Hoek) (2003, 042818) examined associations between air pollution and all-cause (nonaccidental), cardiovascular, COPD, and pneumonia deaths in the entire Netherlands, the four major cities combined, and the entire country minus the four major cities for the period 1986-1994. The air pollutants analyzed included BS, PM_{10}, O_3, NO_2, SO_2, CO, SO_4^{2-} and NO_3^-. In the single-pollutant models, all of the pollutants were significantly associated with nonaccidental mortality at lag 1-day and 0-6 days when using the entire Netherlands data set. In the two-pollutant model, CO risk estimates were reduced to null when PM_{10}, BS, SO_4^{2-} and NO_3^- were included in the model, while the risk estimates for these copollutants remained significantly positive. BS, CO, and NO_2 were highly correlated ($r > 0.85$) in this data set, and the authors noted "all these pollutants should be interpreted as indicators for motorized traffic emissions" (Hoek et al., 2000, 010350). The authors found that O_3 showed the most consistent and independent associations with mortality and that the risk estimates for all of the pollutants were substantially higher in the summer months than in the winter months. Pneumonia deaths showed the largest risk estimates for most pollutants including CO. The result from the Hoek et al. (2000, 010350) study is somewhat in

contrast to the result from the Samoli et al. (2007, 098420) multicity study in that in the Hoek et al. (2000, 010350) analysis, CO was more sensitive to the addition of PM indices in copollutant models. This may be due to the high correlation between CO and PM indices in The Netherlands.

Hoek et al. (2001, 016550) (reanalysis by Hoek) (2003, 042818) analyzed The Netherlands data using more specific cardiovascular causes of death: MI and other IHD, arrhythmia, heart failure, cerebrovascular mortality, and embolism/thrombosis. In this analysis, the authors analyzed O_3, BS, PM_{10}, CO, SO_2, and NO_2 in only single-pollutant models. For all of the pollutants, risk estimates were larger for arrhythmia, heart failure, and cerebrovascular mortality than for the combined cardiovascular mortality outcome. Thus, the results suggested larger impacts of air pollution on more specific cardiovascular causes; however, it is difficult to distinguish the effects of each pollutant from the larger air-pollution mixture.

5.6.1.5. Summary of Mortality and Short-Term Exposure to CO

The recently available multicity studies, which consist of larger sample sizes, along with the single-city studies evaluated reported associations that are generally consistent with the results of the studies evaluated in the 2000 CO AQCD (U.S. EPA, 2000, 000907). However, to date the majority of the literature has not conducted extensive analyses to examine the potential influence of model selection, effect modifiers, or confounders on the association between CO and mortality.

The multicity studies reported comparable CO mortality risk estimates for total (nonaccidental) mortality, with the APHEA2 European multicity study (Samoli et al., 2007, 098420) showing slightly higher estimates for cardiovascular mortality in single-pollutant models. However, when examining potential confounding by copollutants these studies consistently showed that, although CO mortality risk estimates remained positive, they were reduced when NO_2 was included in the model. But this observation may not be confounding in the usual sense in that NO_2 may also be an indicator of other pollutants or pollution sources (e.g., traffic).

Of the studies evaluated, only the APHEA2 study focused specifically on the CO-mortality association (Samoli et al., 2007, 098420), and, in the process, examined: (1) model sensitivity; (2) the CO-mortality concentration-response (C-R) relationship; and (3) potential effect modifiers of CO mortality risk estimates. The sensitivity analysis indicated an approximate 50-80% difference in CO risk estimates from a reasonable range of alternative models, which suggests that some model uncertainty likely influences the range of CO mortality risk estimates obtained in the studies evaluated. The examination of the CO-mortality concentration-response relationship found very weak evidence for a CO threshold at 0.5 mg/m^3 (0.43 ppm). Finally, when examining a variety of city-specific variables to identify potential effect modifiers of the CO-mortality relationship, the APHEA2 study found that geographic region explained most of the heterogeneity in CO mortality risk estimates.

The results from the single-city studies are generally consistent with the multicity studies in that some evidence of a positive association was found for mortality upon short-term exposure to CO. However, the CO-mortality associations were often but not always attenuated when copollutants were included in the regression models. In addition, limited evidence was available to identify cause-specific mortality outcomes (e.g., cardiovascular causes of death) associated with short-term exposure to CO.

The evidence from the recent multi- and single-city studies suggests that an association between short-term exposure to CO and mortality exists. But limited evidence is available to evaluate cause-specific mortality outcomes associated with CO exposure. In addition, the attenuation of CO risk estimates which was often observed in copollutant models contributes to the uncertainty as to whether CO is acting alone or as an indicator for other combustion-related pollutants. Overall, the epidemiologic evidence is **suggestive of a causal relationship between relevant short-term exposures to CO and mortality.**

5.6.2. Epidemiologic Studies with Long-Term Exposure to CO

The 2000 CO AQCD (U.S. EPA, 2000, 000907) did not evaluate the association between long-term exposure to CO and mortality because there were no studies at the time that examined this relationship. Since then there have been several new studies that examined the association between long-term exposure to CO and mortality. It should be noted, however, that these studies focused

primarily on PM, and that CO was only considered in these studies as a potential confounder. Therefore, the information available from these new long-term exposure studies is somewhat limited, especially in comparison to that for PM. Table 5-24 lists the U.S.-based studies evaluated that examined the association between long-term exposure to CO and mortality, along with the mean CO concentrations reported in each study.

Table 5-24. Range of CO concentrations reported in U.S.-based studies that examine mortality effects associated with long-term exposure to CO.

Study	Location	Years	Averaging Time	Mean Concentration (ppm)	Upper Percentile Concentrations (ppm)
Jerrett et al. (2003, 087380)	107 US cities	1980	Annual avg	1.56	Maximum: 3.95
Pope et al. (2002, 024689)	1980: 113 US cities 1982-1998: 122 US cities	1980 1982-1998	Annual avg	1980: 1.7 1982-1998: 1.1	NR
Krewski et al. (2009, 191193)	108 US cities	1980	Annual avg	1.68	75th: 2.13 90th: 2.58 95th: 3.05 Maximum: 3.95
Miller et al. (2007, 090130)	36 US cities	2000	Annual avg	NR	NR
Lipfert et al. (2000, 004087)	US	1960-1974 1975-1981 1982-1988 1989-1996	Mean annual 95th percentile of hourly CO values	1960-1974: 10.82 1975-1981: 7.64 1982-1988: 3.42 1989-1996: 2.36	1960-1974 50th: 9.31 Maximum: 35.3 1975-1981 50th: 7.04 Maximum: 22.4 1982-1988 50th: 3.33 Maximum: 15.20 1989-1996 50th: 2.30 Maximum: 7.10
Lipfert et al. (2006, 088756)	US	1999-2001	Mean annual 95th percentile of hourly CO values	1.63	Maximum: 6.7
Lipfert et al. (2006, 088218)	US	1976-1981 1982-1988 1989-1996 1997-2001	Mean annual 95th percentile of hourly CO values	1976-1981: 7.6 1982-1988: 3.4 1989-1996: 2.4 1997-2001: 1.6	NR
Lipfert and Morris (2002, 019217)	1960-1969: 44 US counties 1970-1974: 206 US counties 1979-1981: 272 US counties 1989-1991: 246 US counties 1995-1997: 261 US counties	1960-1969 1970-1974 1979-1981 1989-1991 1995-1997	Mean annual 95th percentile of hourly CO values	1960-1969: 13.8 1970-1974: 9.64 1979-1981: 5.90 1989-1991: 2.69 1995-1997: 1.72	NR

5.6.2.1. U.S. Cohort Studies

American Cancer Society Cohort Studies

Pope et al. (1995, 045159) investigated associations between long-term exposure to PM and mortality outcomes in the ACS cohort. In this study, ambient air pollution data from 151 U.S. metropolitan areas in 1981 were linked with individual risk factors in 552,138 adults who resided in these areas when enrolled in the prospective study in 1982; death outcomes were ascertained through 1989. $PM_{2.5}$ and SO_4^{2-} were associated with total (nonaccidental), cardiopulmonary, and lung cancer mortality, but not with mortality for all other causes (i.e., nonaccidental minus cardiopulmonary and lung cancer). Gaseous pollutants were not analyzed in Pope et al. (1995, 045159). Jerrett et al. (2003,

087380), using data from Krewski et al. (2000, 012281), conducted an extensive sensitivity analysis of the Pope et al. (1995, 045159) ACS data, augmented with additional gaseous pollutants data. Due to the smaller number of CO monitors available compared to SO_4^{2-}, the number of metropolitan statistical areas (MSAs) included in the CO analysis were reduced (from 151 with SO_4^{2-} to 107). The mean annual CO concentrations in these MSAs ranged from 0.19 to 3.95 ppm. CO was weakly negatively correlated with SO_4^{2-} (r = -0.07). Among the gaseous pollutants examined (CO, NO_2, O_3, SO_2), only SO_2 showed positive associations with mortality, and, in addition, was the only copollutant that reduced SO_4^{2-} risk estimates. For CO, the relative risk estimates for total (nonaccidental) mortality in single- and copollutant models with SO_4^{2-} was 0.99 (95% CI: 0.96-1.01) and 0.98 (95% CI: 0.96-1.01), respectively, per 0.5 ppm increase in mean annual average CO concentrations.

Pope et al. (2002, 024689) conducted an extended analysis of the ACS cohort with double the follow-up time (to 1998) and triple the number of deaths compared to the original Pope et al. (2002, 024689) study. In addition to $PM_{2.5}$, data for all of the gaseous pollutants were retrieved for the extended period and analyzed for their associations with mortality-specific outcomes. As in the 1995 analysis, the air-pollution exposure estimates were based on the MSA-level averages. The authors found that $PM_{2.5}$ and SO_4^{2-} were both associated with all-cause, cardiopulmonary, and lung cancer mortality.[1] In this study, the CO analysis used two different data sets: the first data set consisted of 1980 data and 113 MSAs; while the second data set used averages of the years 1982-1998 and 122 MSAs. The authors found, when using the 1980 data, that CO was not associated (risk estimates ~ 1) (Figure 5-19) with all-cause, cardiopulmonary, lung cancer, or mortality for all other causes. However, the analysis of the 1982-1998 data found that CO was negatively (and significantly) associated with all-cause, cardio-pulmonary, and lung cancer mortality. It is unclear why significant negative associations were observed when analyzing the 1982-1998 data, but evidence from other mortality studies that examined the association between long-term exposure to CO and mortality do not suggest that CO elicits a protective effect.

Krewski et al. (2009, 191193) further analyzed the ACS cohort by adding two additional years of mortality data (total period 1982-2000). This study extended the range of the analysis to incorporate sophisticated adjustment for bias and confounding as well as intra-urban analyses. However, the CO analysis was limited to using (1) nationwide data; (2) only 1980 CO concentrations; and (3) the standard Cox proportional hazards model. In addition to the death categories examined in Pope et al. (2002, 024689), this analysis also examined IHD mortality. As was the case with the Pope et al. (2002, 024689) analysis, Krewski et al. (2009, 191193) found that 1980 CO data was not associated with any of the mortality categories examined: all-cause mortality HR=1.00 (95%CI: 0.99-1.01); cardio-pulmonary mortality, HR=1.00 (95% CI: 0.99-1.00); and IHD mortality, HR=1.00 (95% CI: 0.99-1.01) per 0.5 ppm increase in CO.

Women's Health Initiative Cohort Study

Miller et al. (2007, 090130) studied 65,893 postmenopausal women between the ages of 50 and 79 yr without previous CVD in 36 U.S. metropolitan areas from 1994 to 1998. The authors examined the association between one or more fatal or nonfatal cardiovascular events and air-pollutant concentrations. Exposures to air pollution were estimated by assigning the year 2000 mean concentration of air pollutants measured at the nearest monitor to the location of residence of each subject on the basis of its five-digit ZIP code centroid, which allowed estimation of effects due to both within-city and between-city variation of air pollution. The investigators excluded monitors whose measurement objective focused on a single point source or those with "small measurement scale (0-100 m)." Thus, presumably, these criteria reduced some of the exposure measurement error associated with monitors that are highly impacted by local sources.

During the course of the study, a total of 1,816 women had one or more fatal or nonfatal cardiovascular event, including 261 cardiovascular-related deaths. Hazard ratios for the initial cardiovascular event were estimated. The following results are for models that included only subjects with nonmissing exposure data for all pollutants (n = 28,402 subjects, resulting in 879 CVD events). In the single-pollutant models, $PM_{2.5}$ showed the strongest associations with CVD events among all pollutants (HR = 1.24 [95% CI: 1.04-1.48] per 10 $\mu g/m^3$ increase in annual average), followed by

[1] These results were presented graphically in Pope et al. (2002, 024689) and were estimated for Figure 5-19.

SO_2 (HR = 1.07 [95% CI: 0.95-1.20] per 5 ppb increase in the annual average). For CO the single-pollutant risk estimate was slightly (but not significantly) negative (HR = 0.96 [95% CI: 0.84-1.10]). In the multipollutant model, which included all pollutants (i.e., $PM_{2.5}$, $PM_{10-2.5}$, SO_2, NO_2, and O_3), the CO risk estimate was similar to the one presented in the single-pollutant model (HR = 0.96 [95% CI: 0.82-1.14]). In addition, CO was not associated with CVD events in a single pollutant model (HR = 1.00 [95% CI: 0.90-1.10] per 0.5 ppm increase in mean annual average CO concentration) that used all available observations. Overall this study found that $PM_{2.5}$ was clearly the best predictor of cardiovascular events.

The Washington University-EPRI Veterans' Cohort Mortality Studies

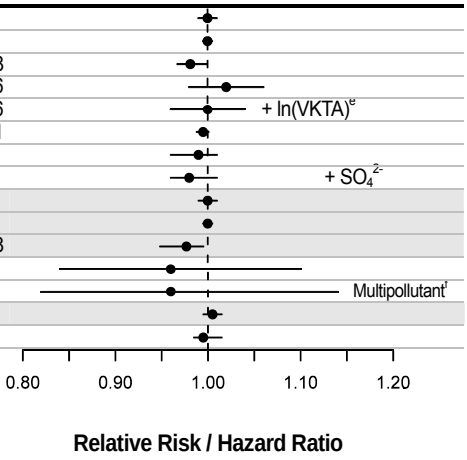
Lipfert et al. (2000, 004087) conducted an analysis of a national cohort of ~70,000 male U.S. military veterans who were diagnosed as hypertensive in the mid-1970s and were followed for approximately 21 yr (up to 1996). Demographically, 35% of the cohort consisted of African-American men and 57% of the cohort was defined as current smokers; however, 81% of the cohort had been smokers at one time in their life. The study examined mortality effects in response to long-term exposure to multiple pollutants, including, $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$, TSP, SO_4^{2-}, CO, O_3, NO_2, SO_2, and Pb. Lipfert et al. (2000, 004087) estimated exposures by indentifying the county of residence at the time of entry to the study. Four exposure periods (1960-1974, 1975-1981, 1982-1988, and 1989-1996) were defined, and deaths during each of the three most recent exposure periods were considered. The mean annual 95th percentile of hourly CO values during these periods declined from 10.8 ppm to 2.4 ppm. The authors noted that the pollution risk estimates were sensitive to the regression model specification, exposure periods, and the inclusion of ecological and individual variables. Lipfert et al. (2000, 004087) reported that indications of concurrent mortality risks (i.e., associations between mortality and air quality for the same period) were found for NO_2 and peak O_3. The estimated CO mortality risks were all negative, but not significant.

Lipfert et al. (2006, 088756) examined associations between traffic density and mortality in the same Veterans' Cohort; however, in this analysis, the follow-up period was extended to 2001. As in their 2000 study, four exposure periods were considered, but more recent years were included in the 2006 analysis. The authors used the mean annual average of the 95th percentile of 24-h avg CO in each of the exposure periods as the averaging metric. The traffic-density variable was the most significant predictor of mortality in their analysis, remaining so in two- and three pollutant models with other air pollutants (i.e., CO, NO_2, O_3. $PM_{2.5}$, SO_4^{2-}, non-SO_4^{2-} $PM_{2.5}$, and $PM_{10-2.5}$). In the multipollutant models, mortality-risk estimates were not statistically significant for any of the other pollutants, except O_3. The natural log of the traffic-density variable (VKTA = vehicle-km traveled per yr) was not correlated with CO (r = -0.06) but moderately correlated with $PM_{2.5}$ (r = 0.50) in this data set. For the 1989-1996 data period, the estimated mortality relative risk was 1.02 (95% CI: 0.98-1.06) per 1 ppm increase in the mean annual 95th percentile of hourly CO concentration in a single-pollutant model. The two-pollutant model, which included the traffic-density variable, resulted in a relative risk of 1.00 (95% CI: 0.96-1.04). Lipfert et al. (2006, 088218) noted that the low risk estimates for CO in this study were consistent with those observed in other long-term exposure studies and may have been due to the localized nature of CO, which can lead to exposure errors when data from centralized monitors is used to represent an entire county. Interestingly, as Lipfert et al. (2006, 088756) pointed out, the risk estimates due to traffic density did not vary appreciably across these four periods, even though regulated tailpipe emissions declined during the study period. The authors speculated that some combination of other environmental factors such as road dust, psychological stress, and noise (all of which constitute the environmental effects of vehicular traffic), along with spatial gradients in SES, might contribute to the nonnegative effects observed.

Lipfert et al. (2006, 088218) extended the analysis of the Veterans Cohort data to include the EPA's Speciation Trends Network (STN) data, which collected chemical components of $PM_{2.5}$. The authors analyzed the STN data for the year 2002 and again used county-level averages. In addition, they analyzed $PM_{2.5}$ and gaseous pollutants data for 1999-2001. As in the other Lipfert et al. (2006, 088218) study, traffic density was the most important predictor of mortality, but associations were also observed for EC, vanadium (V), nickel (Ni), and NO_3^-. Ozone, NO_2, and PM_{10} also showed positive but weaker associations. The authors found no association between the mean annual 95th percentile of hourly CO values and mortality (RR = 0.995 [95% CI: 0.988-1.001] per 1 ppm increase

in CO concentration) in a single-pollutant model. The study did not present copollutant model results for CO.

Cause-specific Mortality	Study	Cohort	Years of Mortality Data	Year(s) of AQ Data
All-cause	Pope et al. (2002, 024689)[a]	ACS	1982-1998	1980
	Krewski et al. (2009, 191193)	ACS	1982-2000	1980
	Pope et al. (2002, 024689)[a]	ACS	1982-1998	1982-98
	Lipfert et al. (2006, 088218)	Veterans	1976-2001	1989-96
	Lipfert et al. (2006, 088218)	Veterans	1976-2001	1989-96
	Lipfert et al. (2006, 088756)	Veterans	1997-2001	1999-01
	Jerrett et al. (2003, 087380)	ACS	1982-1998	1982[c]
	Jerrett et al. (2003, 087380)	ACS	1982-1998	1982[c]
Cardiopulmonary	Pope et al. (2002, 024689)[a]	ACS	1982-1998	1980
	Krewski et al. (2009, 191193)	ACS	1982-2000	1980
	Pope et al. (2002, 024689)[a]	ACS	1982-1998	1982-98
Cardiovascular	Miller et al. (2007, 090130)[b]	WHI	1994-1998	2000
	Miller et al. (2007, 090130)[b]	WHI	1994-1998	2000
IHD	Krewski et al. (2009, 191193)	ACS	1982-2000	1980
Lung Cancer	Krewski et al. (2009, 191193)	ACS	1982-2000	1980



[a]The study does not present CO results quantitatively. This effect estimate and 95% confidence interval were estimated from Figure 5 in Pope et al. (2002, 024689).
[b]Effect estimate is only for subjects with non-missing exposure data for all pollutants.
[c]The study did not report the range of years of CO data used; however, it does specify that air quality data was obtained from pollution monitoring stations operating in 1982.
[d]Unless otherwise specified, all results represent single pollutant models
[e]Natural log of Vehicle-km Traveled variable.
[f]Multipollutant model consisted of CO + $PM_{2.5}$, $PM_{10-2.5}$, SO_2, NO_2, O_3.

Figure 5-19. Summary of mortality risk estimates for long-term exposure to CO. Estimates were standardized to 0.5 ppm and 1.0 ppm for studies that used mean annual average CO and the mean annual 95th percentile of hourly CO values exposure metrics, respectively.

5.6.2.2. U.S. Cross-Sectional Analysis

An ecological cross-sectional analysis involves regressing county- (or city-) average health outcome values on county-average explanatory variables such as air pollution and census statistics. Unlike the cohort studies described above, to the extent that individual level confounders are not adjusted for, the cross-sectional study design is considered to be subject to ecologic confounding. However, all of the cohort studies described above are also semi-ecologic in that the air-pollution exposure variables are ecologic (Kunzli and Tager, 1997, 086180). In this sense, cross-sectional studies may be useful in evaluating the correlation among exposure variables.

Lipfert and Morris (2002, 019217) conducted ecological cross-sectional regressions for U.S. counties (except Alaska) during five periods: 1960-1969, 1970-1974, 1979-1981, 1989-1991, and 1995-1997. They regressed age-specific (15-44, 45-64, 65-74, 76-84, and 85+ yr) all-cause (excluding AIDS and trauma) mortality on air pollution, demography, climate, SES, lifestyle, and diet. The authors analyzed TSP, PM_{10}, $PM_{2.5}$, SO_4^{2-}, SO_2, CO, NO_2, and O_3. However, air pollution data was only available for limited periods of time depending on the pollutant: TSP up to 1991; PM_{10} between 1995 and 1999; and $PM_{2.5}$ between 1979 and 1984 and for 1999. In response to the varying number of counties with valid air pollution data by pollutant and time, Lipfert and Morris (2002, 019217) employed a staged-regression approach. In the first stage, a national model was developed for each dependent variable, excluding air pollution variables. In the second stage, regressions were performed with the residuals on concurrent and previous periods' air pollution variables to identify the pollutants of interest. Many results were presented because of the large number of age groups, lagged-exposure time windows, and mortality study periods examined in the study; overall, the results were similar to those presented in the ACS cohort studies (i.e., $PM_{2.5}$ and SO_4^{2-} were found to be consistently and positively associated with mortality). Lipfert and Morris (2002, 019217) generally found the strongest associations in the earlier time periods and when mortality and air quality were measured in different periods (e.g., mortality data 1995-1997 and CO data 1970-1974).

Also, consistent with the Lipfert et al. (2000, 012281) and the Pope et al. (2002, 024689) cohort studies, CO was frequently negatively (and often significantly) associated with mortality in older age groups, especially when mortality was matched with CO levels in more recent time periods. The younger age group (15-44 yr) often showed a positive association with CO, but considering the small number of deaths attributed to this age group (<1% of total deaths), the association was not informative. Overall, this study highlighted that the CO-mortality associations presented in purely ecologic study designs are generally consistent with those found in semi-individual cohort studies.

5.6.2.3. Summary of Mortality and Long-Term Exposure to CO

The evaluation of new epidemiologic studies conducted since the 2000 CO AQCD (U.S. EPA, 2000, 000907) that investigated the association between long-term exposure to CO and mortality consistently found null or negative mortality risk estimates. No such studies were discussed in the 2000 CO AQCD (U.S. EPA, 2000, 000907). The reanalysis of the ACS data (Pope et al., 1995, 045159) by Jerrett et al. (2003, 087380) found no association between long-term exposure to CO and mortality. Similar results were obtained in an updated analysis of the ACS data (Pope et al., 2002, 024689) when using earlier (1980) CO data; however, negative associations were found when using more recent (1982-1998) data. These results were further confirmed in an extended analysis of the ACS data (Krewski et al., 2009, 191193). The Women's Health Initiative Study also found no association between CO and CVD events (including mortality) using the mortality data from recent years (1994-1998) (Miller et al., 2007, 090130), while the series of Veterans Cohort studies found no association or a negative association between mean annual 95th percentile of hourly CO values and mortality (Lipfert et al., 2006, 088218; Lipfert et al., 2006, 088756). An additional study (Lipfert and Morris, 2002, 019217) was identified that used a cross-sectional study design, which reported results for a study of U.S. counties that were generally consistent with the cohort studies: positive associations between long-term exposure to $PM_{2.5}$ and SO_4^{2-} and mortality, and generally negative associations with CO. Overall, the consistent null and negative associations observed across epidemiologic studies which included cohort populations encompassing potentially susceptible populations (i.e., postmenopausal women and hypertensive men) combined with the lack of evidence for respiratory and cardiovascular morbidity outcomes following long-term exposure to CO; and the absence of a proposed mechanism to explain the progression to mortality following long-term exposure to CO provide supportive evidence that there is **not likely to be a causal relationship between relevant long-term exposures to CO and mortality.**

5.7. Susceptible Populations

Interindividual variation in human responses indicates that some populations are at increased risk for the detrimental effects of ambient exposure to an air pollutant (Kleeberger and Ohtsuka, 2005, 130489). The NAAQS are intended to provide an adequate margin of safety for both general populations and sensitive subgroups, or those individuals potentially at increased risk for health effects in response to ambient air pollution (Section 1.1). To facilitate the identification of populations at the greatest risk for CO-related health effects, studies have evaluated factors that contribute to the susceptibility and/or vulnerability of an individual to CO. The definition for both of these terms varies across studies, but in most instances "susceptibility" refers to biological or intrinsic factors (e.g., lifestage, gender) while "vulnerability" refers to nonbiological or extrinsic factors (e.g., visiting a high-altitude location, medication use) (Table 5-25). Additionally, in some cases, the terms "at-risk" and sensitive populations have been used to encompass these concepts more generally. However, in many cases a factor that increases an individual's risk for morbidity or mortality effects from exposure to an air pollutant (e.g., CO) can not be easily categorized as a susceptibility or vulnerability factor. For example, a population that is characterized as having low SES, traditionally defined as a vulnerability factor, may have less access to healthcare resulting in the manifestation of disease (i.e., a susceptibility factor). But they may also reside in a location that results in exposure to higher concentrations of an air pollutant, increasing their vulnerability. Therefore, the terms "susceptibility" and "vulnerability" are intertwined and at times cannot be distinguished from one another.

As a result of the inconsistencies in the definitions of "susceptibility" and "vulnerability" presented in the literature as well as the inability to clearly delineate whether an identified factor increases an individual's susceptibility or vulnerability to an air pollutant, in this ISA, the term "susceptible population" will be used as a blanket term and defined as follows:

> *Populations that have a greater likelihood of experiencing health effects related to exposure to an air pollutant (e.g., CO) due to a variety of factors including, but not limited to: genetic or developmental factors, race, gender, lifestage, lifestyle (e.g., smoking status and nutrition) orpreexisting disease, as well as population-level factors that can increase an individual's exposure to an air pollutant (e.g., CO) such as socioeconomic status [SES], which encompasses reduced access to health care, low educational attainment, residential location, and other factors.*

Table 5-25. Range of definitions of "susceptible" and "vulnerable" in the CO literature.

Definition	Reference
Susceptible: predisposed to develop a noninfectious disease Vulnerable: capable of being hurt; susceptible to injury or disease	Merriam-Webster (2009, 192146)
Susceptible: greater likelihood of an adverse outcome given a specific exposure, in comparison with the general population. Includes both host and environmental factors (e.g., genetics, diet, physiologic state, age, gender, social, economic, and geographic attributes). Vulnerable: periods during an individual's life when they are more susceptible to environmental exposures.	American Lung Association (2001, 016626)
Susceptible: those who are more likely to experience adverse effects of CO exposure than normal healthy adults (e.g., persons with cardiovascular disease, COPD, reduced or abnormal hemoglobin, older adults, neonates).	U.S. EPA (2008, 193995)
Susceptible: greater or lesser biological response to exposure. Vulnerable: more or less exposed.	U.S. EPA (2009, 192149)
Vulnerable: to be susceptible to harm or neglect, that is, acts of commission or omission on the part of others that can wound.	Aday (2001, 192150)
Susceptible: may be those who are significantly more liable than the general population to be affected by a stressor due to life stage (e.g., children, the elderly, or pregnant women), genetic polymorphisms (e.g., the small but significant percentage of the population who have genetic susceptibilities), prior immune reactions (e.g., individuals who have been "sensitized" to a particular chemical), disease state (e.g., asthmatics), or prior damage to cells or systems (e.g., individuals with damaged ear structures due to prior exposure to toluene, making them more sensitive to damage by high noise levels). Vulnerable: differential exposure and differential preparedness (e.g., immunization).	U.S. EPA (2003, 192145)
Susceptible: intrinsic (e.g., age, gender, preexisting disease (e.g., asthma) and genetics) and extrinsic (previous exposure and nutritional status) factors.	Kleeberger and Ohtsuka (2005, 130489)

To examine whether air pollutants (e.g., CO) differentially affect certain populations, epidemiologic studies conduct stratified analyses to identify the presence or absence of effect modification. A thorough evaluation of potential effect modifiers may help identify populations that are more susceptible to an air pollutant (e.g., CO). Although the design of toxicological and controlled human exposure studies does not allow for an extensive examination of effect modifiers, the use of animal models of disease and the study of individuals with underlying disease or genetic polymorphisms do allow for comparisons between subgroups. Therefore, the results from these studies, combined with those results obtained through stratified analyses in epidemiologic studies, contribute to the overall weight of evidence for the increased susceptibility of specific populations to an air pollutant (e.g., CO).

The remainder of this section discusses the epidemiologic, controlled human exposure, and toxicological studies evaluated in previous sections of Chapter 5 that provide information on potentially susceptible populations. The studies highlighted include only those studies that presented stratified results (e.g., males versus females or <65 yr versus ≥ 65 yr). This approach allows for a direct comparison between populations exposed to similar CO concentrations and within the same study design to determine whether a factor increases the susceptibility of a population to CO-related health effects. In addition, numerous studies that focus on only one potentially susceptible population can provide supporting evidence on susceptibility and are described in Sections 5.2

through 5.6; however, these studies are not discussed in detail in this section. It is recognized that by using this approach to identify potentially susceptible populations, some individuals with underlying medical conditions (i.e., reduced O_2-carrying capacity or elevated COHb levels) or lifestyle characteristics may not be identified due to the lack of studies focusing on these populations. Discussion of conditions affecting CO uptake and elimination as well as endogenous CO production is presented in Sections 4.4 and 4.5, respectively.

5.7.1. Preexisting Disease

The 2000 CO AQCD (U.S. EPA, 2000, 000907) identified certain populations within the general population that may be more susceptible to the effects of CO exposure, including individuals (particularly older adults) with CHD and other vascular diseases, anemia, or COPD. As discussed in the 2000 CO AQCD (U.S. EPA, 2000, 000907) and reviewed in Section 4.5 of this assessment, diseases that cause inflammation and systemic stress are known to increase endogenous CO production, which could potentially increase the susceptibility of individuals with such conditions to health effects induced by ambient CO exposure. The level of COHb that results in the manifestation of health effects varies depending on health outcome and disease state of individuals. The following sections summarize the evidence presented in the 2000 CO AQCD (U.S. EPA, 2000, 000907) along with new evidence which identifies populations with various preexisting diseases that may be susceptible to CO-induced health effects.

5.7.1.1. Cardiovascular Disease

Controlled exposures to CO resulting in COHb concentrations of 2-6% have been shown to affect cardiovascular function among individuals with CAD. Several studies have reported significant decreases in the time to onset of exercise-induced angina or ST-segment changes following CO exposure in patients with stable angina. In the largest such study (Allred et al., 1989, 013018; Allred et al., 1989, 012697; Allred et al., 1991, 011871), COHb concentrations as low as 2.0-2.4% were observed to significantly decrease the time required to induce ST-segment changes indicating myocardial ischemia ($p = 0.01$) (Section 5.2.4). In addition to the effects of CO on myocardial ischemia, there is some evidence to suggest that CO may provoke cardiac arrhythmia in patients with CAD; however, this has not been observed at COHb concentrations below 6% (Sheps et al., 1990, 013286). While healthy adults have been shown to experience a decrease in exercise performance following or during exposure to CO, no changes in cardiac rhythm or ECG parameters have been demonstrated.

Evidence of CO-induced health effects in individuals with CAD is coherent with results from epidemiologic studies that examined the effect of preexisting cardiovascular conditions, through either secondary diagnoses or underlying comorbidities, on associations between CO and ED visits and HAs. Mann et al. (2002, 036723) found increased associations between CO and IHD HAs in individuals with secondary diagnoses of either CHF or dysrhythmia in southern California. Peel et al. (2007, 090442) also examined the effect of underlying cardiovascular conditions on cardiovascular-related HAs in response to short-term exposure to air pollutants, including CO in Atlanta, GA. Individuals with underlying dysrhythmia were found to have increased HAs for IHD, but unlike Mann et al. (2002, 036723), underlying CHF was not found to increase IHD HAs. Peel et al. (2007, 090442) also examined other underlying conditions and found increased HAs for additional cardiovascular effects not specifically related to IHD, including: dysrhythmia, PVCD, and CHF in individuals with underlying hypertension; dysrhythmia and PVCD in individuals with underlying CHF; and PVCD in individuals with underlying dysrhythmia. Although there is no evidence for a clear pattern of CO-induced cardiovascular effects among individuals without CAD across the epidemiologic studies evaluated, the available evidence suggests that underlying dysrhythmia increases IHD HAs in response to short-term exposure to CO.

Additional evidence for increased CO-induced cardiovascular effects not specifically related to IHD is provided by toxicological studies that used animal models of cardiovascular disease. These studies have demonstrated that short-term exposure to 50 ppm CO in rats exacerbates cardiomyopathy and vascular remodeling related to pulmonary hypertension (Carraway et al., 2002, 026018; Gautier et al., 2007, 096471; Melin et al., 2002, 037502; 2005, 193833). Although the population at risk for primary pulmonary hypertension is low, secondary pulmonary hypertension is

a frequent complication of COPD (Section 5.7.1.2) and certain forms of heart failure. These studies demonstrate the potential for short-term exposure to CO to adversely affect individuals with underlying cardiovascular conditions.

The combined evidence from controlled human exposure and epidemiologic studies provides coherence and biological plausibility for the association between CO and cardiovascular morbidity in individuals with CAD, particularly those with IHD. Approximately 13.7 million people in the U.S. have been diagnosed with CAD (also known as CHD), some fraction of whom have IHD (Table 5-26). These individuals, therefore, represent a large population that may be more susceptible to ambient CO exposure than the general population. In addition, the continuous nature of the progression of CAD and its close relationship with other forms of cardiovascular disease suggest that a larger population than just those individuals with a prior diagnosis of CAD may be susceptible to health effects from CO exposure.

Table 5-26. Adult U.S. population in 2007 with respiratory diseases and cardiovascular diseases.

Chronic Condition/ Disease	Adults (18+)	Percentage of U.S. Adult Population by Age					Percentage by Region			
COPD[a]	**(Millions)**	**All (18+)**	**18-44**	**45-64**	**65-74**	**75+**	**NE**	**MW**	**S**	**W**
Chronic bronchitis	7.6	3.4	2.3	4.2	5.5	4.8	2.8	3.2	4.0	2.9
Emphysema	3.7	1.6	0.2	2.3	4.5	5.2	1.1	1.8	1.8	1.6
Cardiovascular Diseases[b]	**(Millions)**	**All (18+)**	**18-44**	**45-64**	**65-74**	**75+**	**NE**	**MW**	**S**	**W**
All heart disease[c]	25.1	11.2	4.1	12.2	27.1	35.8	10.6	12.3	11.3	10.2
Coronary heart disease[d]	13.7	6.1	0.9	6.7	18.6	23.6	5.3	6.7	6.4	5.5
Hypertension	52.9	23.2	8.2	32.1	50.9	57.4	21.3	23.4	25.1	21.0
Stroke	5.4	2.4	0.3	2.8	6.3	10.6	2.2	2.3	2.7	2.2

[a] Respondents were asked if they had ever been told by a doctor or other health professional that they had emphysema. In a separate question, respondents were asked if they had been told by a doctor or other health professional in the last 12 mo that they had bronchitis. A person may be represented in more than one row.
[b] In separate questions, respondents were asked if they had ever been told by a doctor or other health professional that they had: hypertension (or high blood pressure), coronary heart disease, angina (or angina pectoris), heart attack (or myocardial infarction), any other heart condition or disease not already mentioned, or a stroke. A person may be represented in more than one row.
[c] Heart disease includes coronary heart disease, angina pectoris, heart attack, or any other heart condition or disease.
[d] Coronary heart disease includes coronary heart disease, angina pectoris, or heart attack.

Source: National Health Interview Survey, 2007, Tables 1-4 (Pleis and Lucas, 2009, 202833).

5.7.1.2. Obstructive Lung Disease

COPD is a progressive disease resulting in decreased air flow to the lungs and which is especially prevalent among smokers. O_2 limitation resulting from this reduction in air flow may exacerbate CO-related O_2 limitation and subsequent cardiovascular or respiratory effects in individuals with COPD. The national prevalence of chronic bronchitis and emphysema, the two main forms of COPD, was estimated to be 7.6 million and 3.7 million people in 2007, respectively (Table 5-26), although there could be overlap among these two populations. The 2000 CO AQCD (U.S. EPA, 2000, 000907) identified individuals with obstructive lung diseases, such as COPD, as a susceptible population due to a majority of COPD patients having exercise limitations as demonstrated by a decrease in O_2 saturation during mild to moderate exercise. This may heighten the sensitivity of these individuals to CO during submaximal exercise typical of normal daily activity. In addition, COPD patients who are smokers may have elevated baseline COHb levels of 4-8% (U.S. EPA, 2000, 000907). COPD is often accompanied by a number of changes in gas exchange, including increased V_D and V_A/Q inequality (Marthan et al., 1985, 086334), which could slow both CO uptake and elimination.

The few epidemiologic studies of cardiovascular effects in individuals with underlying COPD show weak positive associations between ambient CO and increased CVD HAs or ED visits. For example, Peel et al. (2007, 090442) found that associations between short-term CO exposure and HAs for PVCD or CHF were increased in individuals with a secondary diagnosis of COPD. However, underlying COPD was not associated with increased IHD or dysrhythmia HAs. As

described in Section 5.7.1.1, animal toxicological studies demonstrate CO-induced exacerbation of vascular remodeling related to pulmonary hypertension, a form of which is a frequent complication of COPD.

A controlled human exposure study of respiratory effects in individuals with COPD (Bathoorn et al., 2007, 193963), found that two of the patients experienced COPD exacerbation during or following CO exposure at 100-125 ppm for 2 h, although a slight anti-inflammatory effect was also observed. Although the majority of the evidence for CO-induced effects comes from studies that focus on individuals with COPD, epidemiologic studies also report weak positive associations for asthmatics (Section 5.5.2.2) who can also experience exercise-induced airflow limitation. In addition, preliminary evidence from a recent animal toxicological study indicates mild pulmonary inflammation in response to 50 ppm CO (Ghio et al., 2008, 096321). Since pulmonary inflammation plays an important role in the exacerbation of COPD and asthma, it may serve as a mechanism underlying CO-induced respiratory effects; however, additional research is needed to confirm these results. Taken together, the limited evidence from epidemiologic and controlled human exposure studies and some preliminary evidence from toxicological studies suggests that individuals with obstructive lung disease (e.g., COPD patients with underlying hypoxia, asthmatics) may be susceptible to cardiovascular or respiratory effects due to CO exposure.

5.7.1.3. Diabetes

Exhaled CO concentrations are elevated in individuals with diabetes and are correlated with blood glucose levels and duration of disease, indicating increased endogenous CO production (Section 4.5). As a result, it has been speculated that elevated baseline COHb levels in diabetic individuals could increase the susceptibility of diabetics to CO-induced health effects in response to ambient CO exposures. Epidemiologic studies provide evidence which suggests that diabetics are at increased risk for cardiovascular ED visits and HAs compared to nondiabetics in response to short-term exposure to CO (Pereira Filho et al., 2008, 190260; Zanobetti and Schwartz, 2001, 016710). This is consistent with results reported by Peel et al. (2007, 090442), who observed an increase in cardiovascular-related ED visits for dysrhythmias and PVCD in individuals with diabetes but not for IHD or CHF ED visits. The results from Peel et al. (2007, 090442) that indicate an increase in dysrhythmia ED visits for individuals with diabetes are consistent with results from a panel study conducted by Min et al. (2009, 199514) to investigate the relationship between CO and HRV in individuals with metabolic syndrome. Metabolic syndrome is characterized by risk factors for both diabetes and CVD, including elevations in blood pressure, fasting blood glucose, triglycerides, and waist circumference, as well as low levels of HDL cholesterol. Min et al. (2009, 199514) observed associations between short-term exposure to CO and changes in HRV parameters among subjects with metabolic syndrome but not among healthy subjects. In addition, the observed associations were robust in copollutant models with either PM_{10} or NO_2. In an analysis of individual risk factors, the CO effects were stronger among subjects with higher levels of fasting blood glucose or triglycerides. Although no evidence was identified from controlled human exposure or toxicological studies regarding CO exposure and diabetes, vascular dysfunction was demonstrated in an animal model of metabolic syndrome and was attributed to increased endogenous CO production (Johnson et al., 2006, 193874). Thus, increased endogenous CO production and the potential for higher baseline COHb concentrations, combined with the limited epidemiologic evidence showing cardiovascular effects, suggests that diabetics are potentially susceptible to short-term exposure to CO.

5.7.1.4. Anemia

Although no controlled human exposure or epidemiologic studies were identified that specifically examined CO-related health effects in individuals with anemia, the 2000 CO AQCD (U.S. EPA, 2000, 000907) suggested that conditions such as anemia that produce tissue hypoxia by lowering the blood O_2 carrying capacity or content will result in a greater risk of effects from COHb-induced hypoxia due to the combined effects of both sources of hypoxia. As discussed in Section 4.4.4 of this ISA, anemias are a group of diseases that lower hematocrit and result in reduced arterial O_2 content due to Hb deficiency through hemolysis, hemorrhage, or reduced hematopoiesis. Hereditary hemoglobinopathies such as sickle cell anemia and thalassemia also reduce the O_2-carrying capacity of the blood. Anemia may also result from pathologic conditions characterized by

chronic inflammation such as malignant tumors or chronic infections (Cavallin-Ståhl et al., 1976, 086306; Cavallin-Ståhl et al., 1976, 193239). The cardiovascular system of people with anemia compensates for the reduction in O_2 carrying capacity by increasing cardiac output as both heart rate and stroke volume increase. One of the most prevalent forms of anemia arises from a single-point mutation in the Hb gene, resulting in sickle cell diseases. The affinity of Hb for O_2 and its O_2 carrying capacity is reduced, causing a shift to the right in the O_2 dissociation curve. It is well documented that African-American populations have a higher incidence of sickle cell anemia, which may be a risk factor for effects due to CO-mediated hypoxia. Other hereditary hemoglobinopathies, such as thalassemia, also reduce the O_2-carrying capacity of the blood due to the production of an abnormal form of hemoglobin. Overall, lowered hematocrit due to anemia may result in increased susceptibility and a greater response to inhalation of ambient CO.

Anemia may also increase the susceptibility of an individual to CO exposure in a different manner through the increased production of endogenous CO as a result of the disturbance of RBC hemostasis by accelerated destruction of hemoproteins (Section 4.5). Pathologic conditions such as hemolytic anemias, hematomas, thalassemia, Gilbert's syndrome with hemolysis, and other hematological diseases and illness will accelerate endogenous CO production (Berk et al., 1974, 012386; Hampson and Weaver, 2007, 190272; Meyer et al., 1998, 047530; Solanki et al., 1988, 012426; Sylvester et al., 2005, 191954). Patients with hemolytic anemia exhibit COHb levels at least two- to threefold higher than healthy individuals and CO production rates two- to eightfold higher (Coburn et al., 1966, 010984). Recent studies report elevated COHb levels of 4.6-9.7% due to drug-induced hemolytic anemia (Hampson and Weaver, 2007, 190272) and between 3.9% and 6.7% due to an unstable hemoglobin disorder (Hb Zürich) (Zinkham et al., 1980, 011435). Taken together, this evidence suggests that individuals with anemia who have diminished O_2-carrying capacity and/or high baseline COHb levels may be more susceptible to health effects due to ambient CO exposure, although no studies were identified that evaluated specific CO-related health effects in anemic individuals.

5.7.2. Lifestage

Age alters the variables that influence the uptake, distribution, and elimination of CO (Section 4.4.3). COHb levels decline more rapidly in young children compared to adults after CO exposure (Joumard et al., 1981, 011330; Klasner et al., 1998, 087196). After infancy, the COHb half-life increases with age, practically doubling between the ages of 2 and 70 yr (Joumard et al., 1981, 011330). However, it should be noted that the rate of this reduction in CO elimination is very rapid in the growing years (2-16 yr of age) but slows beyond adolescence. An increase in alveolar volume and D_LCO were observed with increasing body length of infants and toddlers (Castillo et al., 2006, 193234); these changes suggest faster CO uptake due to more advanced lung development. After infancy, increasing age decreases D_LCO and increases V_A/Q mismatch, resulting in a longer duration for both loading and elimination of CO from the blood (Neas and Schwartz, 1996, 079363).

5.7.2.1. Older Adults

The 2000 CO AQCD (U.S. EPA, 2000, 000907) noted that changes in metabolism that occur with age, particularly declining maximal oxygen uptake, may make the aging population susceptible to the effects of CO via impaired oxygen delivery to the tissues. Several epidemiologic studies compared cardiovascular outcomes in older and younger adults, although no such studies were conducted in the U.S. In a study in Australia and New Zealand, Barnett et al. (2006, 089770) found an increase in IHD and MI HAs among individuals ≥ 65 yr of age compared with individuals aged 15-64 yr in response to short-term exposure to CO. Lee et al. (2003, 095552) also found an association with IHD HAs in Seoul, Korea, for individuals ≥ 65 yr of age but not when all individuals were included in the analysis. Lanki et al. (2006, 089788) found an association with HAs for nonfatal MI in a multicity European study among those aged ≥ 75 yr but not for those <75 yr old. In contrast, D'Ippoliti et al. (2003, 074311) observed higher associations for MI hospital admissions in Rome among 18- to 64-yr olds than among either 65- to 74-yr olds or those 75 yr and over. Szyszkowicz (2007, 193793) found slightly lower associations for IHD hospital admissions in Montreal, Canada among those >64 yr of age than for the all-age group. Another Canadian study (Fung et al., 2005, 074322) conducted in Windsor, Ontario, found some evidence of increased

associations for between CO and CVDs (defined as HF, IHD, or dysrhythmia) among individuals ≥ 65 yr of age compared with the <65-yr age group. No controlled human exposure studies or toxicological studies were identified that compared CO effects among older and younger adults or animal models of senescence, respectively. Overall, the epidemiologic studies evaluated provide limited evidence that older adults may be susceptible to CO exposure.

A combination of factors may be responsible for increased susceptibility to CO-related health effects among older adults. One important factor which may contribute to the observed increases in CO-induced cardiovascular effects is the much higher prevalence of CAD and other cardiovascular conditions in older adults compared with the general population. As shown in Table 5-26,18.6% of adults aged 65-74 yr and 23.6% of adults aged 75 yr and over reported having CHD, as compared with 6.1% of the population as a whole. Both the higher prevalence of CAD and the gradual decline in physiological processes associated with aging (U.S. EPA, 2006, 192082) may contribute to increased health effects in response to CO in this population. Older adults represent a large and growing fraction of the U.S. population, from 12.4% or 35 million people in 2000 to a projected 19.3% or 72 million people in 2030 (U.S. Census, 2000, 157064), and, as a result, are a large population that is potentially susceptible to CO-induced health effects.

5.7.2.2. Gestational Development

CO inhaled by pregnant animals quickly crosses the placental barriers and enters fetal circulation. Effects of ambient CO may be enhanced during gestation because fetal CO pharmacokinetics do not follow the same kinetics as maternal CO exposure; this contributes to the difficulty in estimating fetal COHb based on maternal levels. It has been demonstrated that human fetal Hb has a higher affinity for CO than adult Hb (Di Cera et al., 1989, 193998). Maternal and fetal COHb concentrations have been modeled as a function of time using a modified CFK equation (Hill et al., 1977, 011315). At steady-state conditions, fetal COHb has been found to be 10-15% higher than maternal COHb levels. For example, exposure to 30 ppm CO results in a steady-state maternal COHb of 5% and a fetal COHb of 5.75%. Fetal CO uptake lags behind maternal uptake for the first few hours but later may overtake the maternal values. Similarly, during washout, fetal COHb levels are maintained for longer, with a half-life of around 7.5 h versus the maternal half-life of around 4 h (Longo and Hill, 1977, 010802). In addition, maternal endogenous CO production increases during pregnancy (0.92 mL/h) due to contributions from fetal endogenous CO production (0.036 mL/h) and altered hemoglobin metabolism (Hill et al., 1977, 011315; Longo, 1970, 013922).

Epidemiologic studies provide limited evidence that in utero CO exposure is associated with changes in various birth outcomes (Section 5.4.1). CO exposure during early pregnancy was associated with an increased risk of PTB. In the studies that examined associations between CO and birth defects, maternal CO exposure was associated with an increased risk of cardiac birth defects, which is also coherent with evidence in Section 5.2 identifying the heart as a target organ for CO. There is also evidence for small reductions in birth weight (10-20 g) associated with CO exposure, generally in the first or third trimester, although the decrease does not generally translate to an increased risk of LBW or SGA. It is therefore difficult to conclude if CO is related to a small change in birth weight across all births or a marked effect in some subset of births. In addition, there is limited evidence that prenatal CO exposure is associated with an increased risk of infant mortality in the post-neonatal period.

Toxicological studies lend biological plausibility to the CO-related developmental outcomes observed in epidemiologic studies (Section 5.4.2). Associations have been observed between CO exposure in laboratory animals and decrements in birth weight as well as reduced prenatal growth. Animal toxicological studies also provide evidence for effects on the heart, including transient cardiomegaly at birth after continuous in utero CO exposure and delayed myocardial electrophysiological maturation. Evidence exists for additional developmental outcomes which have been examined in toxicological studies but not epidemiologic or human clinical studies, including behavioral abnormalities, learning and memory deficits, locomotor effects, neurotransmitter changes, and changes in the auditory system. Furthermore, exogenous CO may interact or disrupt the normal physiological roles of endogenous CO in the body. There is evidence that CO plays a role in maintaining pregnancy, controlling vascular tone, regulating hormone balance, and sustaining normal follicular maturation.

The developmental outcomes examined in the epidemiologic studies evaluated affect a substantial portion of the U.S. population. PTB and LBW have been established as strong predictors

of infant mortality and morbidity (Barker et al., 2002, 193960; Berkowitz and Papiernik, 1993, 055466; Li et al., 2003, 193965; McIntire et al., 1999, 015310). In 2004, 36.5% of all infant deaths in the U.S. were preterm-related (MacDorman et al., 2007, 193973). Vital statistics for the year 2005 in the U.S. showed that the rate for PTB was 12.7%, which has risen 20% since 1990, and the rate for LBW was 8.2%, which has risen 17% since 1990 (Martin et al., 2007, 193982). Data from the Metropolitan Atlanta Congenital Defects Program (MACDP), which is one of the most comprehensive birth defect registries in the U.S., have shown that the prevalence of congenital heart defects increased between 1968 and 1997. During 1995-1997 the rate was 90.2 per 10,000 births (0.9%) and this was an increase of 58.7 per 10,000 births above the rate during 1968-1972 (Botto et al., 2001, 192379). Cardiovascular defects are the single largest contributor to infant mortality attributable to birth defects (CDC, 1998, 193243). Between 1995 and 1997, 1 in 13 infant deaths (7.4%) was due to a congenital heart defect (Boneva et al., 2001, 193972). The combined evidence from epidemiologic and toxicological studies, along with the increasing prevalence of PTB, LBW, and cardiac birth defects in the U.S. population, indicates that critical developmental phases may be characterized by enhanced sensitivity to CO exposure.

5.7.3. Gender

COHb concentrations are generally higher in male subjects than in female subjects (Horvath et al., 1988, 012725). In addition, the COHb half-life is longer in healthy men than in women of the same age, which may be partially explained by differences in muscle mass or the slight correlation between COHb half-life and increased height (Joumard et al., 1981, 011330). The rate of decline of D_LCO with age is lower in middle-aged women than in men; however, it is similar in older adults (Neas and Schwartz, 1996, 079363). Lower rates of decline in lung diffusing capacity are consistent with the observation that women tend to be more resistant than men to altitude hypoxia (Horvath et al., 1988, 012725). Women also experience fluctuating COHb levels through the menstrual cycle when endogenous CO production doubles in the progesterone phase (0.62 mL/h versus 0.32 mL/h in estrogen phase) (Delivoria-Papadopoulos et al., 1974, 086316; Mercke and Lundh, 1976, 086309). Similarly, endogenous CO production increases during pregnancy due to contributions from fetal CO production and altered hemoglobin metabolism as described above. In an epidemiologic study investigating the association between short-term CO exposure and IHD hospital admissions (Szyszkowicz, 2007, 193793), males had higher associations than females in both the all-ages group and in those >64 yr of age. However, this limited epidemiologic evidence combined with known gender-related differences in endogenous CO production do not provide sufficient basis for determining whether CO disproportionately affects males or females.

5.7.4. Altitude

Higher altitude results in changes in a number of factors that contribute to the uptake and elimination of CO. The relationship between altitude and CO exposure has been discussed in depth in the 2000 CO AQCD (U.S. EPA, 2000, 000907) and other documents (U.S. EPA, 1978, 086321) and is reviewed in Section 4.4.2 of this ISA. In an effort to maintain proper O_2 transport and supply, physiological changes occur as compensatory mechanisms to combat the decreased barometric pressure and resulting altitude-induced hypobaric hypoxia. These changes, which include increases in BP and cardiac output and redistribution of blood from skin to organs and from blood to extravascular compartments, generally will favor increased CO uptake and COHb formation, as well as CO elimination. It has been demonstrated that breathing CO (9 ppm) at rest at altitude produces higher COHb compared to sea level (McGrath et al., 1993, 013865), whereas high-altitude exposure in combination with exercise causes a decrease in COHb levels versus similar exposure at sea level (Horvath et al., 1988, 012725). This decrease could be a shift in CO storage or suppression of COHb formation, or both. In a controlled human exposure study on the health effects of CO at altitude, Kleinman et al. (1998, 047186) observed that CO exposure and simulated high altitude reduced the time to onset of angina relative to clean-air exposure at sea level by 9% and 11%, respectively, among a group of individuals with CAD. In this study, the combined effects of altitude and CO exposure were observed to be additive, with subjects experiencing, on average, an 18% decrease in the time to onset of angina following exposure to CO and simulated altitude relative to clean air

exposure at sea level. No epidemiologic studies were identified that specifically examined the effect of altitude on health effects due to CO exposure.

Altitude also increases the baseline COHb levels by inducing endogenous CO production and has been shown to be positively associated with baseline COHb concentrations (McGrath, 1992, 001005; McGrath et al., 1993, 013865). This increase in COHb with altitude-induced hypoxia has also been associated with increases in mRNA, protein, and activity of HO-1 in rats and cells leading to enhanced endogenous CO production (Carraway et al., 2002, 026018; Chin et al., 2007, 190601). Early HH has been found to increase lung HO-1 protein and activity, whereas chronic HH induced endogenous CO production in nonpulmonary sites (Section 4.5) (Carraway et al., 2000, 021096). Whether other variables (such as an accelerated metabolism or a greater pool of Hb, transient shifts in body stores, or a change in the elimination rate of CO) play a role in increasing COHb concentrations at high altitudes has not been explored.

As the length of stay increases at high altitude, acclimatization occurs, inducing hyperventilation, polycythemia or increased red blood cell count, and increased tissue capillarity and Mb content in skeletal muscle, which could also favor increased CO uptake. Most of the initial adaptive changes gradually revert to sea-level values. However, these adaptive changes persist in people raised at high altitude even after reacclimatization to sea level (Hsia, 2002, 193857). This evidence indicates that visitors to high altitude locations may represent a potentially susceptible population for increased risk of health effects due to CO exposure.

5.7.5. Exercise

Exercise is an important determinant of CO kinetics and toxicity due to the extensive increase in gas exchange. O_2 consumption can increase more than 10-fold during exercise. Similarly, ventilation, membrane and lung diffusing capacity, pulmonary capillary blood volume, and cardiac output increase proportional to work load. The majority of these changes facilitate CO uptake and transport by increasing gas exchange efficiency. Likewise, the COHb elimination rate increases with physical activity, causing a decrease in COHb half-life (Joumard et al., 1981, 011330). The potential effects of CO on exercising individuals was demonstrated in a controlled human exposure study where healthy subjects exposed to CO achieved COHb levels of approximately 5%, which resulted in a significant decrement in exercise duration and maximal effort capability (measured by metabolic equivalent units) (Adir et al., 1999, 001026). These effects could be attributed to CO lowering the anaerobic threshold, allowing earlier fatigue of the skeletal muscles and decreasing maximal effort capability during heavy exercise. Due to the counterbalancing effects of increased rates of COHb formation and elimination, it is unclear whether individuals engaging in light to moderate exercise are a potentially susceptible population for increased health effects due to ambient CO exposure.

5.7.6. Proximity to Roadways

Individuals that spend a substantial amount of time on or near heavily traveled roadways, such as commuters and those living or working near freeways, are likely to be exposed to elevated CO concentrations, as discussed in Chapter 3. Targeted sampling studies have found CO concentrations measured at the roadside to be several-fold higher than concentrations measured a few hundred meters downwind (Baldauf et al., 2008, 191017; Zhu et al., 2002, 041553), with the shape of the concentration profile dependent on wind speed and direction. AQS monitoring data aggregated across multiple sites with no adjustment for wind conditions show somewhat higher concentrations for microscale (near-road) monitors relative to middle-scale monitors, although the ratio is lower than that observed in the roadside studies. Elevated near-road concentrations are important for residents of the estimated 17.9 million occupied homes nationwide (16.1%) that are within approximately 90 m of a freeway, railroad, or airport, according to the 2007 American Housing Survey (2008, 194013).

Studies of commuters have shown that commuting time is an important determinant of CO exposure for those traveling by car, bicycle, public transportation, and walking (Bruinen de Bruin et al., 2004, 190943; Kaur et al., 2005, 086504; Scotto Di Marco et al., 2005, 144054). In-vehicle concentrations have been measured to be several times higher than concentrations measured at fixed-site monitors not located adjacent to roadways (Bruinen de Bruin et al., 2004, 190943; Chang et al., 2000, 001276; Kaur et al., 2005, 086504; Riediker et al., 2003, 043761; Scotto Di Marco et al., 2005,

144054). Commuting is likely to be an important contributor to CO exposure for the 5.5 million U.S. worker (5%) who drive 60 min or more to work (U.S. Census Bureau, 2008, 194013). This evidence for elevated on-road and near-road CO concentrations combined with residential and commuting data indicates that the large numbers of individuals who spend a substantial amount of time on or near heavily traveled roadways are an important population that is potentially susceptible to increased health risks due to ambient CO exposure.

5.7.7. Medications and Other Substances

Endogenous CO production can be altered by medications or a number of physiological conditions that increase RBC destruction, the breakdown of hemoproteins other than Hb, and the production of bilirubin (Section 4.5). Nicotinic acid, allyl-containing compounds (acetamids and barbiturates), diphenylhydantoin, progesterone, contraceptives, and statins increase CO production. One epidemiologic study (Dales, 2004, 099036) investigated the effect of medication use on the relationship between ambient CO and HRV in individuals with CAD. The authors observed an association between short-term CO exposure and an increase in SDNN for CAD patients not taking beta blockers; however, this association did not persist in CAD patients taking beta blockers.

Compounds such as carbon disulfide and sulfur-containing chemicals (parathion and phenylthiourea) increase CO following metabolism by cytochrome p450s. The P450 system may also cause large increases in CO produced from the metabolic degradation of dihalomethanes such as methylene chloride leading to very high (>10%) COHb levels, which can be further enhanced by prior exposure to HCs or ethanol. Minor sources of endogenous CO include the auto-oxidation of phenols, photo-oxidation of organic compounds, and lipid peroxidation of cell membrane lipids. Taken together, this evidence indicates that individuals ingesting medications and other substances that enhance endogenous or metabolic CO production represent a population that is potentially susceptible to increased health effects due to additional exposure to ambient CO.

5.7.8. Summary of Susceptible Populations

Individuals with CAD represent the population most susceptible to increased risk of CO-induced health effects, based on evidence of significant decreases in the time to onset of exercise-induced angina or ST-segment changes observed in controlled human exposure studies of individuals with CAD. This is coherent with the results from epidemiologic studies that observed associations between short-term CO exposure and ED visits and HAs for IHD and related outcomes. The limited evidence from stratified analyses in epidemiologic studies, which indicates that secondary diagnoses of CHF or dysrhythmia modify associations between short-term CO exposure and IHD HAs, provides further support that individuals with cardiovascular disease represent a potentially susceptible population. Additional evidence is provided by toxicological studies that demonstrated exacerbation of cardiomyopathy and increased vascular remodeling in animal models of cardiovascular disease. Although it is not clear whether the small changes in COHb associated with ambient CO exposures result in substantially diminished O_2 delivery to tissues, the known role of CO in limiting O_2 availability provides biological plausibility for ischemia-related health outcomes following CO exposure. The continuous nature of the progression of CAD and its close relationship with other forms of cardiovascular disease suggest that a larger population than just those individuals with a prior diagnosis of CAD may be susceptible to health effects from CO exposure.

Populations potentially susceptible to CO-induced health effects also include individuals with other preexisting diseases, such as COPD or diabetes. Preliminary evidence available from controlled human exposure and epidemiologic studies suggests that individuals with obstructive lung disease may be susceptible to increased cardiovascular or respiratory effects due to CO exposure. Increased endogenous CO production and the potential for higher baseline COHb concentrations in individuals with diabetes, combined with the limited epidemiologic evidence showing cardiovascular effects, suggests that diabetics are potentially susceptible to short-term exposure to CO. Individuals with various types of anemia who have diminished O_2-carrying capacity and/or high baseline COHb levels may be more susceptible to health effects due to ambient CO exposure, although no studies were identified that evaluated specific CO-related health effects in individuals with anemia.

There is also evidence that older adults and the developing young represent populations potentially susceptible to CO-induced health effects. Epidemiologic studies provide limited evidence

from stratified analyses indicating that associations between short-term CO exposure and hospital admissions for CAD are higher among those ≥ 65 yr old than for those <65 yr. The older adult population also has a much higher prevalence of CAD than the general population as a whole, which may contribute to their increased susceptibility. Recent studies on birth outcomes have provided limited evidence of associations between in utero CO exposure and PTB, LBW and cardiac birth defects. Toxicological studies provide evidence of effects on birth weight and growth as well as development of the cardiovascular and nervous systems following prenatal exposure to CO. This evidence, combined with differences between fetal and maternal CO pharmacokinetics, indicates that critical developmental phases may be characterized by enhanced sensitivity to CO exposure.

Visitors to high-altitude locations may represent a potentially susceptible population due to changes in factors which affect the uptake and elimination of CO, although acclimatization occurs as length of stay increases. Individuals with substantial exposure to mobile source emissions, such as commuters and those living near heavily traveled roadways, represent an important population potentially susceptible to increased risk of CO-induced health effects due to elevated on-road and roadside CO concentrations.

Overall, the controlled human exposure, epidemiologic, and toxicological studies evaluated in this assessment provide evidence for increased susceptibility among multiple populations. Medical conditions that increase endogenous CO production rates may also contribute to increased susceptibility to health effects from ambient CO exposure. Although the weight of evidence varies depending on the factor being evaluated, the clearest evidence indicates that individuals with CAD are most susceptible to an increase in CO-induced health effects.

5.8. Summary

The evidence reviewed in this chapter describes recent findings regarding the health effects of ambient CO. Section 5.1 presents evidence on the mode of action of CO, including its role in limiting O_2 availability as well as its role in altered cell signaling. Evidence is presented in subsequent sections on the effect of short- and long-term exposure to CO on cardiovascular morbidity (Section 5.2), the central nervous system (Section 5.3), birth outcomes and developmental effects (Section 5.4), respiratory morbidity (Section 5.5), and mortality (Section 5.6). Potentially susceptible populations at increased risk of CO-induced health effects are discussed in Section 5.7.

Table 2-1 summarizes causal determinations for the health outcome categories reviewed in this assessment. An integrative overview of the health effects of ambient CO and uncertainties associated with interpretation of the evidence is provided in Chapter 2. The strongest evidence regarding CO-induced health effects relates to cardiovascular morbidity, and the combined evidence from controlled human exposure studies and epidemiologic studies indicates that a causal relationship is likely to exist between relevant short-term CO exposures and cardiovascular morbidity, particularly in individuals with CAD. The evidence is suggestive of a causal relationship between short-term exposure to CO and respiratory morbidity as well as between short-term CO exposure and mortality. The evidence is also suggestive of a causal relationship for birth outcomes and developmental effects following long-term exposure to CO, and for central nervous system effects linked to short- and long-term exposure to CO. The evidence indicates that there is not likely to be a causal relationship between long-term exposure to CO and mortality. For respiratory morbidity following long-term exposure to CO, the evidence was inadequate to infer a causal relationship.

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Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at http://epa.gov/hero. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

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